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THIAZOLIUM IONS AND RELATED HETEROAROMATIC SYSTEMS. IV. PRODUCT IDENTIFICATION, KINETICS, AND EQUILIBRIA IN RING-OPENING OF THIAZOLIUM IONS

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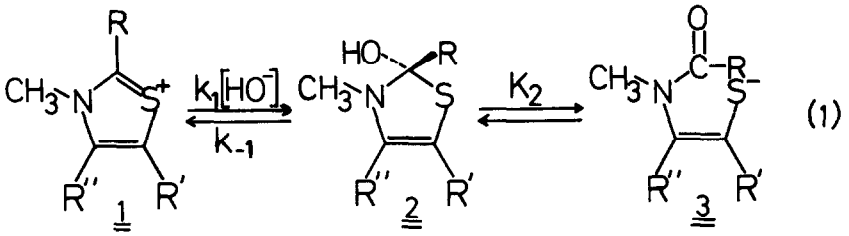
Rapid base-catalyzed exchange of the C-2 proton in thiazolium ions is essential to the catalytic function of thiamine.[1] However, HO^- can also cause opening of this heteroaromatic ring. The sequence in eg. 1 has been proposed for this reaction.[2]

We have studied ring-opening of model thiazolium-ions (1), and we report here evidence on the identity of the product formed initially and contributions to the kinetics, mechanism, and equilibria in this reaction.



1a, 2a, 3a: R=R''=H, R'=CH_3
1b, 2b, 3b: R=R'=CH_3, R''=H
1c, 2c, 3c: R=R''=CH_3, R'=H

When 1a is placed in a pH stat,[3] base is consumed to equilibrium values indicated by the triangles in Fig. 1. That is, there is pH - dependent consumption of base to a maximum of 2 equivalents.[2] We have shown that the immediate product is 3a by pmr spectroscopy. On addition of hydroxide, the pmr absorbances of 1a diminish and new peaks appear at higher field. When two equivalents of hydroxide have been added, the original absorbances have vanished. The new spectrum reveals a formyl hydrogen

at -477 Hz, the 5-H moved to -372 Hz, and the methyl groups split due to hindered rotation about the N-C bond of the amide moiety[4] as the structure of 3a would lead one to expect.[5]

The equilibrium amounts of HO^- consumed indicate an equilibrium involving primarily 1 and 3 with $K_{eq} = [3]/[1][HO^-]^2 = 2 \times 10^9 M.^{-2}$ However, the data do not exclude lower concentrations of 2 and protonated 3.

Rates of consumption of base at constant pH[3] yielded pseudo first-order rate constants. The pH dependence is in Fig. 1 (circles). Above pH 9.9, the reaction is first-order in $[HO^-]$.[6] Using eq 1 and applying the steady state assumption for [2], we obtain eq 2. A good fit (Fig. 1, solid line) to the experimental data is obtained using eq 2 and

$$k_{obs} = k_1 [HO^-] + k_{-1}/(1 + K_2 [HO^-]) \qquad (2)$$

these values of rate and equilibrium constants:

$$k_1 = 23\ M^{-1}\ sec^{-1};\ k_{-1} = 1.5 \times 10^{-2}\ sec^{-1};\ K_2 = 9 \times 10^5\ M^{-1}.$$

Although 2, a tetrahedral intermediate,[7] appears to be present at all pH values in minor concentrations, there is the following evidence that 2 is truly involved: 1) the product is 3; 2) the first-order dependence of the rate on $[HO^-]$ at the higher pH values although two moles of HO^- are consumed in the reaction; 3) the increase in k_{obs} at low pH due to the $1/[OH^-]$ term in eq 2.[8]

Additional proof of attack of HO^- at the 2 position of 1 is obtained from study of two 2-methylated ions, 2b and 2c. Hydroxide is consumed by 2b and 2c 100 times more slowly than by 2a, a reasonable steric and electronic effect for this reaction.[9]

This work has possible significant implications. First, the value of k_1 would indicate considerable kinetic instability of thiazolium ions at physiological pH; the half-life of 1a would be 33 hours at pH 7.4 if step 1 were irreversible. However, because of the equilibrium dependence of $1 \rightleftharpoons 3$ on $[HO^-]^2$, 1 is highly favored at pH 7.4. The integrity of thiamine at physiological pH is based, therefore, on the thermodynamics of eq. 1, not the kinetics. Secondly, the kinetic instability means that there is dynamic interconversion of thiazolium ions with ring-opened forms in biological systems. Membranes may be impermeable to thiazolium ions but permeable to the ring-opened forms.[10]

This would provide a chemical rationale for the evolution of thiamine as a vitamin.

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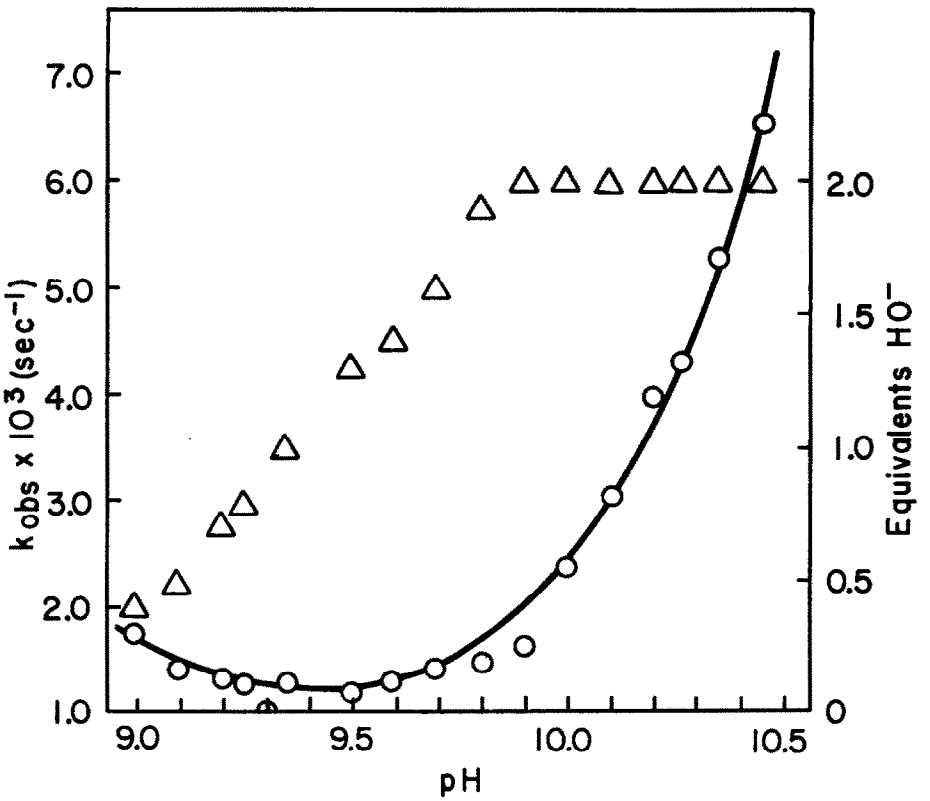

Figure 1. pH-rate profile for thiazolium hydrolysis: O = experimental pseudo-first-order rate constants (left legend); ——— = theoretical curve; Δ = equivalents of HO^- consumed at equilibrium (right legend).

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(3) Using a Radiometer instrument equipped with automatic syringe.

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(5) Chemical shifts relative to tetramethylsilane.

(6) If the first-order dependence is extrapolated to $[HO^-] = 0$, $k_{obs} = 0$. Thus, there is no significant water term in thiazolium hydrolysis under these conditions.

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(8) A complete analysis will be provided in the full paper.

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