Kishi's examples are, with one exception, conformationally mobile acyclic systems, and it is suggested that in cyclic systems the effect of an allylic methyl group is similar to that of a hydroxyl substituent.[16] We believe that the overriding factor governing the course of the osmium tetraoxide oxidation of 8 is the stereoelectronic effect of the quasi-axial allylic alcohol which directs hydroxylation anti to the hydroxyl group. Application of this hypothesis to the systems described by both Kishi[16] and Danishefsky,[17] assuming normal ground-state geometry, gives results which are consistent with those obtained by both authors.[19] Prior to removal of the now unnecessary 3β-hydroxyl group, the 1α,2α-diol was protected as the acetonide. Barton deoxygenation[20] proceeded smoothly to afford **10**, which gave racemic **1**, mp 240–241 °C, on removal of the protecting groups. The NMR, solution IR, and mass spectra of synthetic isocelorbicol were identical with those of the natural product.

This synthesis of (±)-isocelorbicol (**1**) from ketoagarofuran **2** entails 15 steps and proceeds in an overall yield of 3.2% with complete stereoselectivity at each step.

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(18) The allylic alcohol in 8 can become orthogonal to a cation at C-2 if ring A is in a half-boat conformation. However, in this conformation the α-face of the double bond suffers severe hindrance from the angular methyl group. Also, the NMR spectrum of 8 clearly indicates that the ground-state conformation is that with ring A in a half chair.

(19) The decreased stereoselectivity described by Kishi (ref 16) for allylic esters is explained by assuming interaction of the unshared electrons of the allylic oxygen with the ester carbonyl.

(20) Barton, D. H. R.; McCombie, S. W. *J. Chem. Soc., Perkin Trans. 1* **1975**, 1574.

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Reversible Ring-Opening of Thiamine. Kinetic vs. Thermodynamic Control of the Reclosure

Summary: The reversible ring opening and closing of quaternary thiazolium ions (Q^+) is studied, the biphasic behavior observed on reclosure is attributed to N–S acyl transfer, and the results are rationalized in terms of the pH-dependent behavior of the tetrahedral intermediate (T°).

Sir: Various aspects of the chemistry of thiamine (vitamin B_1) are under active investigation.[1] One area which is only partially understood is the reversible ring-opening of the thiazolium ring in aqueous solution[2–4] and its possible role in the transport of thiamine across membranes.[4] Indeed,

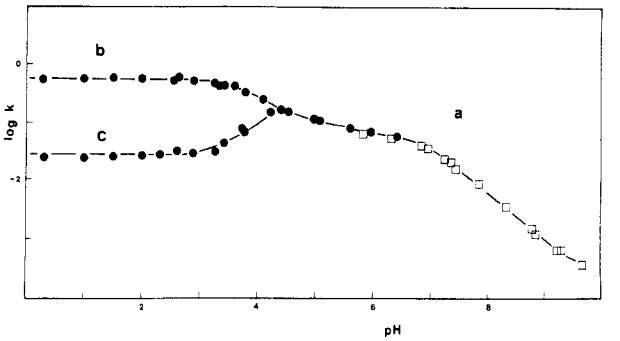
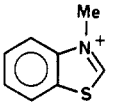


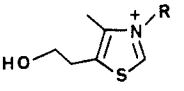
Figure 1. pH–log rate profile for the reclosure of the enethiolate (ETh^-) derived from thiamine ($B1^+$). Units of k are s^{-1}, at 25 °C, I = 1.0 M. Rate constants represented by closed circles were obtained at low buffer strength (0.01 M) by stopped-flow UV spectrophotometry.[5] The open squares are for data obtained by conventional UV measurement of rates extrapolated to zero buffer concentration. The product of processes a and c is thiamine; the product of process b is believed to be the protonated amino thiol ester Es^+. Similar rate profiles have been obtained for reclosure of the thiolates derived from BT^+ and HET^+.

the understanding of this reaction of thiazolium ions in general is relatively limited.

As an approach to these problems we are studying the behavior of thiamine ($B1^+$) and two model ions: the *N*-

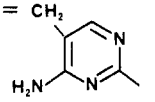


BT^+



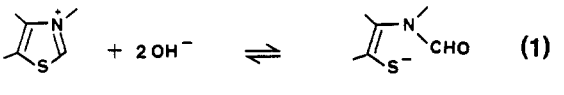
R = Me HET^+

R = CH_2



$B1^+$

methylbenzothiazolium ion (BT^+) and the 3,4-dimethyl-5-(2-hydroxyethyl)thiazolium ion (HET^+), over the whole pH range 0–14 using stopped-flow[5] and conventional UV–vis spectrophotometry. Ring-opening of such quaternary thiazolium ions (Q^+) in basic solution produces amido enethiolates (ETh^-, eq 1), which reclose upon acidifica-



(1)

tion.[2–4] For the equilibrium shown in eq 1 we can define a constant $K^2_{op} = [ETh^-][H^+]^2/[Q^+]$ such that pK_{op} is the pH at which Q^+ and ETh^- are present in equal amounts.[2–4] We now find that reclosure of the enethiolates derived from thiamine and the two model ions at pH < pK_{op} shows one kinetic phase at intermediate pHs but that at low pHs *two* distinct phases are observable.[6]

(1) *Thiamine. Twenty Years of Progress*; Sable, H. Z., Gubler, C. J., Eds.; N.Y. Acad. Sci.: New York, 1982. (*Ann. N.Y. Acad. Sci.* **1982**, *378*, 7–122).

(2) Bunting, J. W. *Adv. Heterocycl. Chem.* **1979**, *25*, 1, and references cited therein.

(3) (a) Zoltewicz, J. A.; Uray, G. *J. Org. Chem.* **1980**, *45*, 2104. (b) Kluger, R.; Chin, J.; Smyth, T. *J. Am. Chem. Soc.* **1981**, *103*, 884. (c) Hopmann, R. F. W. *Ann. N.Y. Acad. Sci.* **1982**, *378*, 32. (d) El Hage Chahine, J. M.; Dubois, J. E. *J. Am. Chem. Soc.* **1983**, *105*, 2335.

(4) Haake, P.; Duclos, J. M. *Tetrahedron Lett.* **1970**, 461. Duclos, J. M.; Haake, P. *Biochemistry* **1974**, *13*, 5358.

(5) Cf. Tee, O. S.; Trani, M.; McClelland, R. A.; Seaman, N. E. *J. Am. Chem. Soc.* **1982**, *104*, 7219.

(6) After the inception of the present work two kinetic phases were noted by others[3d] but they were not studied in detail. Surprisingly, the two phases were not noted by Hopmann.[3c]

(7) In addition to the behavior described in the text, the three systems show very similar rates for the plateau regions of processes b and c, as well as similar activation parameters.

0022-3263/86/1951-2150$01.50/0

Scheme I

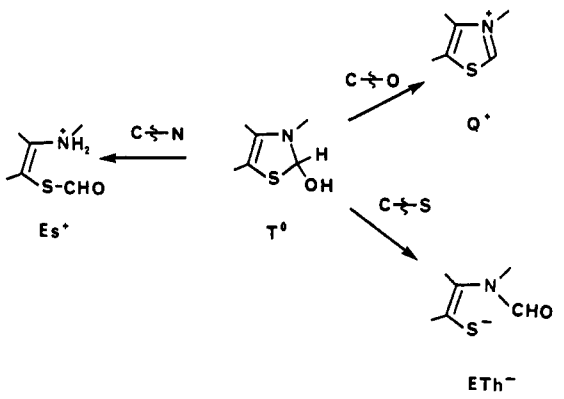


Figure 1 shows the pH–log rate profile obtained for reclosure of the thiolate derived from thiamine at pH ≤ pK_{op} = 9.6. Between pH 4.5 and 9.6 one process (labeled a) is observed which results in the reformation of thiamine. In contrast, below pH 4.5 *two* processes (labeled b and c) are apparent and it is the second of these which reforms the thiazolium ring. Buffer catalysis is observed over the range of process a, the descending limb of process b, and the ascending limb of process c. No such catalysis is found at lower pHs for the plateau regions of processes b and c. Similar behavior is observed for the reclosure of the thiolates from BT^+ and HET^+ and so it is not simply a peculiarity of the thiamine system.

Broadly speaking, the features outlined above can be understood in terms of the formation and breakdown of the tetrahedral intermediate, T°, which is the pseudobase[2] of the thiazolium ion Q^+ (Scheme I). This species can undergo breakdown by C–O, C–N, or C–S bond cleavage, depending upon the pH. In the ring-opening direction T° is formed by rate-limiting attack of hydroxide ion[2-4] on Q^+ and then undergoes fast deprotonation and ring-opening to the enethiolate, ETh^- (C–S bond cleavage).[8]

Process a (Figure 1) involves C–O bond cleavage. Its pH dependence and the associated buffer catalysis can be rationalized by the general acid-catalyzed loss of OH from T° formed in a preequilibrium from ETh^- or its conjugate acid ETh[9] (eq 2). Note, however, that H^+ does not make

$$ETh^- \underset{K_{Th}}{\overset{H^+}{\rightleftharpoons}} ETh \rightleftharpoons T^\circ \xrightarrow{HA} Q^+ \qquad (2)$$

a significant contribution to the catalysis of this breakdown at the pHs involved (4.5–9.6).

The bifurcation of the rate profile around pH 4.5 (Figure 1) is ascribed to the onset of the general acid-catalyzed breakdown of T° to give the amino enethiol ester Es, present as its protonated form Es^+, the product of C–N bond cleavage (Scheme I and eq 3). The process b takes

$$ETh \rightleftharpoons T^\circ \xrightarrow[HA]{H^+} Es \underset{}{\overset{H^+}{\rightleftharpoons}} Es^+ \qquad (3)$$

over from process a because the rate constant for H^+ catalysis of T° to Es is larger than that for T° to Q^+ (vide infra). At pH 3.5 the profile for process b levels out and buffer catalysis disappears; in the region of change curved buffer plots are observed. These findings are consistent with a change of rate-limiting step: at low pH the breakdown of T° is sufficiently fast that its formation becomes rate-limiting.[11]

Process c (Figure 1) is attributed, therefore, to the conversion of Es^+ to the thiazolium ion Q^+, also via the intermediate T° (eq 4). At low pH there is no net catalysis

$$Es^+ \underset{H^+}{\rightleftharpoons} Es \rightleftharpoons T^\circ \xrightarrow[HA]{H^+} Q^+ \qquad (4)$$

observed since the necessary deprotonation of Es^+ cancels with the proton catalysis of T° to Q^+. For similar reasons there is apparent general base-catalysis around pH 4 due to actual specific base/general acid catalysis. Above pH 3.5 the profile for process c rises as proton catalysis of T° to Q^+ is no longer important relative to simple unassisted ionization. It is this lack of catalysis by H^+ which gives rise to the bifurcation of the rate profiles around pH 4.5 (vide supra).

In summary, acidification of solutions of the enethiolates (ETh^-) derived from $B1^+$, BT^+, and HET^+ gives rise to two distinct kinetic phases at low pH. The first (kinetic control) forms, we believe, an amino enethiol ester Es[16] while the second (thermodynamic control) results in the reconstitution of the appropriate thiazolium ring, both processes occurring via the tetrahedral intermediate T°. These finding are not only of relevance to the chemistry of thiamine and other thiazolium ions[1-4] but also to the pH dependent behavior of tetrahedral intermediates in acyl transfer reactions.[12-15,17-19] The conversion of ETh^- to Es is an intramolecular N to S acyl transfer[12,13] similar to those believed to be involved within the enzyme–substrate complexes of various thiol proteases.[20] Moreover, the breakdown of the N,O,S tetrahedral intermediate involved in papain-catalyzed amide hydrolysis is general acid-catalyzed,[20] as found here for T° to Es.

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(8) The behavior of thiamine in aqueous base (pH >9.6) is actually more complicated in that there is prior formation of a "yellow form" (see ref 3c and references therein). However, the overall result is the same, the yellow form being only a temporary diversion.[3c]

(9) From analysis of the data for process a the pK_a of ETh is about 6.7 for thiamine and 7.9 for HET^+. In the case of BT^+ no clear inflection is apparent in the rate profile but from spectra extrapolated to time zero the thiol pK_a is about 5.6, as previously deduced by Vorsanger.[10]

(10) Vorsanger, H. *Bull Soc. Chim. Fr.* **1967**, 551, 556. Related papers on BT^+ by the same author are *Ibid.* **1964**, 3118; *Ibid.* **1967**, 2124.

(11) Similar changes in rate-limiting step have been detected for related reactions involving tetrahedral intermediates.[12-15]

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(15) Aldersley, M. F.; Kirby, A. J.; Lancaster, P. W.; McDonald, R. S.; Smith, C. R. *J. Chem. Soc., Perkin Trans. 2* **1974**, 1487.
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