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Decomposition of 2-(1-Hydroxybenzyl)thiamin. Ruling Out Stepwise Cationic Fragmentation

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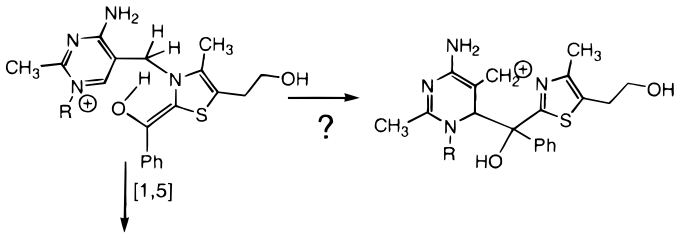
ABSTRACT

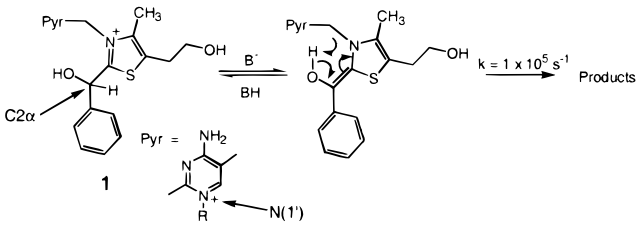


The rapid fragmentation of 2-(1-hydroxybenzyl)thiamin (1) is initiated by transfer of a proton from C2α to give an enamine. The subsequent irreversible process can be written as a concerted (or stepwise) rearrangement involving migration of the hydroxyl hydrogen to the methylene bridge. An attractive alternative is internal addition of C2α to the pyrimidine, generating a carbocation. However, addition of azide to the reaction solution, which could trap the carbocation, has no effect on the rate or products of reaction.

In neutral solution the adduct of thiamin (vitamin B1) and benzaldehyde, 2-(1-hydroxybenzyl)thiamin (HBzT **1**, R = H, an intermediate in the formation of benzoin), undergoes a surprising fragmentation reaction that splits the molecule into its pyrimidine and thiazole components. This overwhelms reversion to thiamin and benzaldehyde. The reaction occurs with oxidation at C2α and is promoted by a positive charge at N(1′).[1,2] We have previously reported results that establish that the loss of the C2α proton, which generates an enamine, is the initial step in the process.[3] This can be rate-determining, and subsequent steps compete with reprotonation. We have determined that the rate constant for fragmentation of the enamine is 1×10^5 s^{-1} and have proposed an electrocyclic mechanism, Scheme 1.

Although the first step in the mechanism is clearly proton abstraction, the nature of subsequent steps has not been established. An intriguing alternative mechanism for fragmentation of the C2α carbanion is shown in Scheme 2. It is a variation of that discovered by Zoltewicz for the sulfite-catalyzed fragmentation of thiamin, which also applies to 2-(1-hydroxyethyl)thiamin (HET).[4] The proposed mechanism involves intramolecular attack of the C2α carbanion at the 6′ position of the pyrimidine ring. Expulsion of the thiazole follows to give the resonance-stabilized cation **2** (Scheme 2). This cation cleaves at C2α−C6′ to give the pyrimidine and the phenyl thiazole ketone (Scheme 2).

Scheme 1



(1) Kluger, R.; Lam, J. F.; Kim, C.-S. *Bioorg. Chem.* **1993**, *21*, 275.
(2) Kluger, R.; Lam, J. F.; Pezacki, J. P.; Yang, C.-M. *J. Am. Chem. Soc.* **1995**, *117*, 11383.
(3) Kluger, R.; Moore, I. F. *J. Am. Chem. Soc.* In press.
(4) Zoltewicz, J. A.; Kauffman, G. M. *J. Am. Chem. Soc.* **1977**, *99*, 3134.

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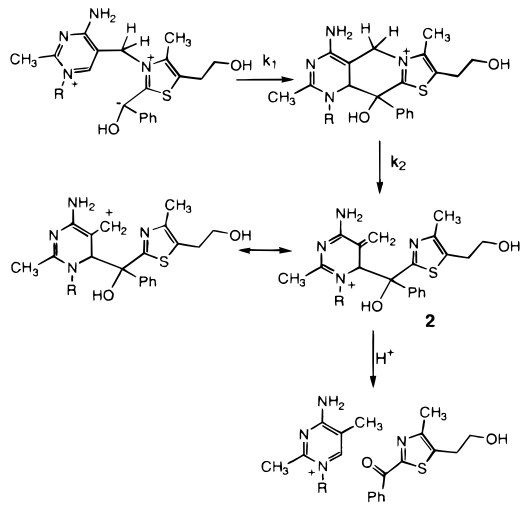
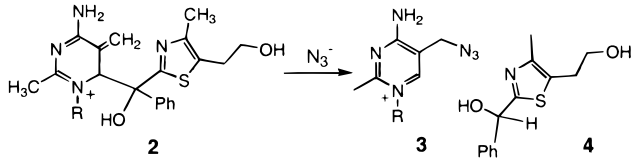
Scheme 2



To distinguish the two mechanisms, we designed an experiment based on Zoltewicz's observation that azide ion can trap a cationic intermediate following addition of a nucleophile to the pyrimidine. Thus, cation **2** would be trapped by addition of azide, giving the azido-substituted pyridinium salt (**3**) and the reduced phenyl thiazole (**4**, Scheme 3).

Scheme 3



N(1′)-MethylHBzT (NMHBzT, R = methyl) (0.040 g) was dissolved in 4.0 mL of 3.0 M sodium azide. The solution was kept at pH 8 (pH-stat). After 3 h, the solution was brought to pH 5. The thiazole fragment was separated from the reaction mixture by extraction. Analysis of the extract by NMR indicated the presence of only the phenyl thiazole ketone. The freeze-dried aqueous layer contained the *N*(1′)-methylpyrimidine but no azidopyrimidine[5] (compared with a synthesized sample).[6]

Azide ion is an efficient cation trapping reagent with second-order rate constants ranging from 5×10^9 M^{-1} s^{-1} to 5×10^5 M^{-1} s^{-1} (the latter for stable cations).[7,8] Using the lower limit for trapping **2**, we obtain a predicted first-order rate constant of 1×10^6 s^{-1} under our experimental conditions. This is fast enough to compete with the fragmentation step ($k = 1 \times 10^5$ s^{-1}).[3] Since no azido product is formed, either intermediate **2** is not formed or it breaks down with a rate constant that is much larger than 1×10^6 s^{-1}. If the latter were the case, then the two steps preceding the breakdown of **2** (k_1 and k_2 in Scheme 2) would have to have rate constants of 1×10^5 s^{-1} or more, which is inconsistent with the reactivity of this type of species: the rate constant for cleavage of 2-1-(hydroxyethyl)thiamin by sulfite is 0.12 M^{-1} s^{-1}, with the addition of sulfite and elimination of the thiazole partially rate-limiting.[3,9]

Thus, our results establish that the fragmentation avoids carbocationic intermediates, which would be trapped by azide. The large rate constant and the lack of trapping indicate that an electrocyclic route for fragmentation should be considered as being likely.[10]

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(5) Singlet at δ 4.6 for (CH_2N_3).

(6) Synthesized by reaction of *N*(1′)-methylthiamin and sodium sulfite (0.1 equiv) in the presence of sodium azide (2.5 equiv). We have estimated the minimum amount detectable by NMR to be 0.1 mg or <0.5% based on NMHBzT.

(7) McClelland, R. A. *Tetrahedron* **1996**, *52*, 6823.

(8) Richard, J. P.; Toteva, M. M.; Crugeiras, J. *J. Am. Chem. Soc.* **2000**, *122*, 1664.

(9) Uray, G.; Celotto, C.; Ibovnik, A.; Zoltewicz, J. A. *J. Org. Chem.* **1989**, *54*, 3941.

(10) Less, A.; Nendel, M.; Wilsey, S.; Houk, K. N. *J. Am. Chem. Soc.* **1999**, *121*, 4524 and references therein.