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REGARDING EXCHANGE OF THE 2-HYDROGEN OF THIAMINE THROUGH THE TETRAHEDRAL INTERMEDIATE FORMED BY NUCLEOPHILIC ADDITION

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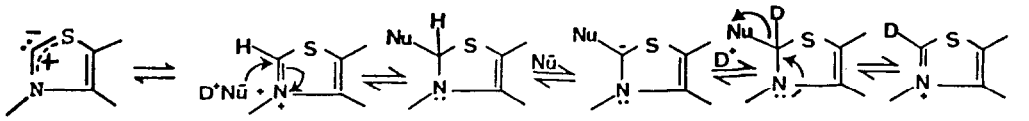
Summary: Kinetic data demonstrates that the exchange of hydrogen at the 2-position of thiazolium ions cannot occur through the tetrahedral intermediate formed by nucleophilic addition of hydroxide to the 2-position.

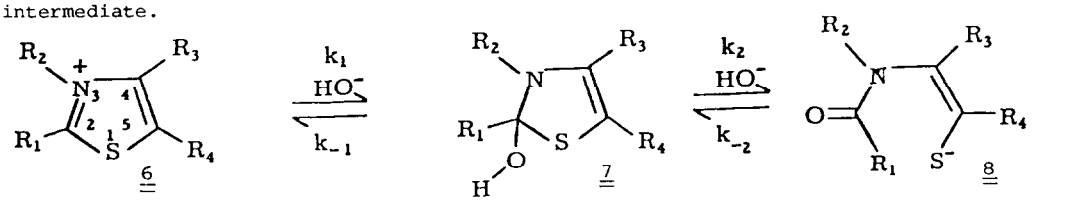
Breslow's discovery[1] of rapid exchange of the 2-hydrogen of thiazolium ions (1) is the key to understanding the mechanism of action of thiamine pyrophosphate,[2] the essential coenzyme for α-keto acid decarboxylose and transketolase. Exchange and thiamine action[3] have been considered to be due to unusual stability of the 2-ylid (2).[2,4] However, a recent communication[5] has suggested that thiazolium ions exchange their 2-hydrogens through the tetrahedral intermediate which is formed by addition of hydroxide or alkoxide at the 2 position:



(1)

2 1 3 4 5

The tetrahedral intermediate (3) has been postulated in the ring-opening reaction of thiamine by Maier and Metzler,[6] then was studied in detail in azolium ions,[7-9] and has recently been studied in detail in a thiamine derivative.[10] All investigations found it difficult to prove the existence of the tetrahedral intermediate beyond doubt because the intermediate (3) never accumulates in detectable amounts. Nevertheless, there is considerable circumstantial evidence which favors ring-opening (eq. 3) via this species.[5-10] For example, we have studied salt effects, solvent deuterium isotope effect, and effects of ring-substituents on rate;[11] all are consistent with ring-opening via the tetrahedral intermediate.



(2)

6 7 8

It is particularly important that the structure of the ring-opened product was proved by nmr spectroscopy[7,8,11] and the equilibrium constant, $K = [8]/[6]$, was shown to dependent on $(1/[HO^-])^2$. Yet, the rate of ring-opening was first order in $[HO^-]$. Because the tetrahedral intermediate (7) should lose the enethiolate anion much more readily than HO^-,

the rate-determining step appears to be $HO^- + \underline{6} \rightarrow \underline{7}$.

The recent proposal, that exchange of 2-hydrogens of thiazolium ions occurs by initial nucleophilic attack at the 2-position, is based upon rates of exchange of thiazolium ions in a series of deuterated alcohols.[5] The rate slowed considerably as the steric size of the alcohol increased; the authors attributed this to steric hindrance to nucleophilic attack of alkoxide at the 2-position. Although we had considered, during our research an opening of thiazolium rings, the possibility that exchange might occur via a pathway involving (7),[11] we rejected the idea because it can be shown to be impossible based on kinetics.

First, note that the process shown in eq. 1 would certainly require that exchange be second order in $[HO^-]$. The carbanion (3) would be expected to be extremely unstable based on other research on carbanion generation.[12] Therefore, formation of the carbanion would be rate-determining. Therefore, two moles of base are required to reach the transition state and exchange through this process would be second order in HO^-. We demonstrated beyond any doubt that exchange is, in fact, first order in hydroxide.[7,11] This alone eliminates the possibility of exchange through this process.[5]

Second, the relative rates of exchange and ring-opening preclude exchange through the tetrahedral intermediate.[4,7] Our studies which showed first order dependence of exchange on $[HO^-]$ gave a second order rate constant of $3.7 \times 10^5 M^{-1}s^{-1}$ at 33°.[4] The study of ring-opening on the same thiazolium ion at essentially the same temperature (30°) gave a second order rate constant (first order in substrate and first order in hydroxide as also found by other authors on similar systems[9,12,13]) considerably smaller, $23\ M^{-1}s^{-1}$.[7] Since the tetrahedral intermediate is formed more than 10^4 times slower than exchange, any exchange through the tetrahedral intermediate must proceed more than 10^4 times slower than the main exchange pathway which, therefore, does appear to involve the 2-ylid.[1,2,4]

Finally, it seems likely that the relative rates of exchange reported by Karimian, et. al.[5] might be due to differences in concentrations of alkoxide ions. t-Butyl alcohol is a much weaker acid (probably by at least 10^3) than methyl alcohol. This effect would lead to a very low concentration of alkoxide ion in t-butyl alcohol and could account for the slow exchange in this solvent even though the 2-ylid mechanism is correct.

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