On the Intramolecular Cyclization of a Thiazolium Salt

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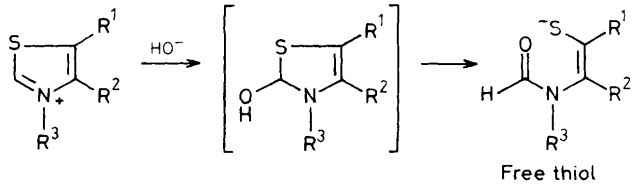
3-Acetonyl-4-methyl-1,3-thiazolium chloride is resistant to basic hydrolysis to its free-thiol form and undergoes instead a unique intramolecular cyclization to yield a stable bicyclic form.

Most thiazolium salts, including thiamine, hydrolyse in basic solution to a corresponding free-thiol form *via* a mechanism involving rate-determining addition of hydroxide to the C-2 position of the thiazolium nucleus (Scheme 1).[1] However, in basic ethanol (or butanol) thiamine (**1**) yields the tricyclic form (**2**) *via* a mechanism involving the addition of the pyrimidinyl-amino group to the C-2 position of the thiazolium ring (Scheme 2).[2] We now report studies on a synthetic thiazolium salt which undergoes a similar intramolecular cyclization reaction in basic aqueous solution.

When the thiazolium salt (**3**) was treated with one equivalent of sodium hydroxide, the resultant bicyclic form (**4**) crystallized from solution in quantitative yield (Scheme 3). The structure of (**4**), which contains a stable thiazoline ring, a unique O,S,N-ortho ester, and a highly stable hemiacetal, was deduced from elemental analysis, and the mass spectral, ^{1}H and ^{13}C n.m.r. data.† During the formation of (**4**) in solutions varying from pH 9 to 13, we were unable to detect the presence of the corresponding free-thiol form of (**3**) by either u.v. or n.m.r. spectroscopy; this is the first example of a thiazolium salt that is resistant to base hydrolysis.

In contrast to the tricyclic form of thiamine, the bicyclic species (**4**) is stable in both acidic and basic aqueous solutions. After three days at pH 1 only 30% of (**4**) is converted into thiazolium salt (**3**), whereas even after seven days at pH 5 this conversion was not detected. Under basic conditions there was no decomposition of (**4**) as determined by thin-layer chromatography and ^{1}H and ^{13}C n.m.r. spectroscopy. Even at pH 13, conditions under which the hemiacetal is deprotonated, (**4**) does not decompose with production of the free-thiol form.

The kinetics of formation of (**4**) were studied spectrophotometrically. This reaction is first order in thiazolium salt and second order in hydroxide, and the pseudo-first order rate constant for the intramolecular cyclization reaction of (**3**) in 10 mM borate buffer at pH 9.4 is 1.2×10^{-2} s^{-1}. A reaction mechanism involving addition of a hydrate dianion to C-2 of the thiazolium ring is consistant with these kinetic data

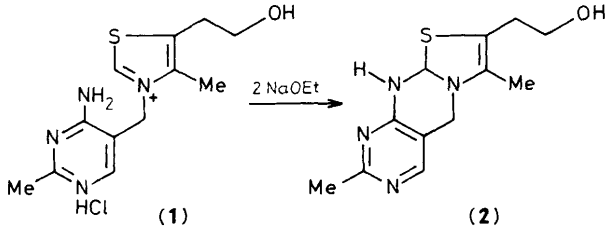


Scheme 1

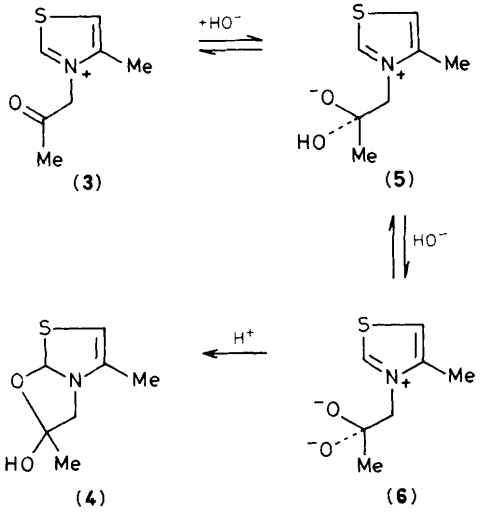
† Satisfactory analytical data were obtained for (**4**) and (**5**). *Spectroscopic data* (**5**): 360 MHz ^{1}H n.m.r. ([$^2H_6$]acetone) δ 8.6 (s,1H, ortho ester-H), 5.3 (s, 1H, vinyl-H), 5.2 (s, 1H, OH), 4.4 (d, 1H, CH_2), 3.2 (d, 1H, CH_2), 2.1 (s, 3H, vinyl-CH_3), 1.5 (s, 3H, CH_3); 360 MHz; ^{13}C n.m.r. ([$^2H_6$]acetone) δ 160.6 (ortho ester-C), 128.2 (C=*C*–N), 100.5 (S–*C*=C), 76.4 (hemiacetal-C), 50.3 (CH_2), 28.1 (CH_3), 20.7 (vinyl-CH_3); mass (chemical ionization) *m/z* 174 ($M^+ + 1$), 156 ($M^+ + 1 - H_2O$), 100 (4-methylthiazole nucleus).

(Scheme 3). The second deprotonation of (**5**) to (**6**) would be necessary if the rate of the intramolecular cyclization of the hydrate anion (**5**) is too slow to compete with the rapid rate of reversion of (**5**) to (**3**). The intermediacy of hydrate dianions has been invoked to explain the second order dependence on hydroxide in the alkaline hydrolysis of acetylacetone,[3] 3-ketodihydrobenzothiophene-1-dioxide,[4] and 2-ketoalkylpyridinium salts.[5] A dianion mechanism has also been proposed by Biechler and Taft to account for the second order dependence on hydroxide in the alkaline hydrolysis of trifluoroacetanilides.[6]

In summary, as a consequence of both the intramolecular cyclization pathway and the stability of (**4**) in basic solution, the thiazolium salt (**3**) is resistant to base hydrolysis to the corresponding free-thiol form. This result raises an interesting point concerning a possible role for the tricyclic form of thiamine pyrophosphate (TPP) in enzymic systems. Crosby and Lienhard[7] and Hoppman *et al.*[8] have argued that, to be effective catalysts, enzymic systems must decrease the pK_a of the C-2 proton of TPP relative to its pK_a in aqueous solution.[7] By whatever mechanism this might be achieved, the thiazolium ring of TPP would also be rendered more susceptible to



Scheme 2



Scheme 3

hydrolysis to the catalytically inactive free-thiol form.‡ One can envisage that selective formation of the tricyclic species of TPP might be one mechanism by which this undesirable hydrolytic reaction could be prevented. Additionally, in contrast to the slow conversion of the bicyclic species (**4**) into the thiazolium salt (**3**), protonation of N-7 of the tricyclic species would ensure an enzyme-controlled mechanism for rapid formation of the catalytically active thiazolium form of TPP.

We acknowledge Professor E. T. Kaiser for his financial support and for his discussions during the course of this investigation. We also thank Professor F. J. Kezdy for his helpful suggestions. D. S. L. acknowledges an N.I.H. postdoctoral fellowship.

Received, 17th October 1984; Com. 1463

‡ Duclos and Haake (ref. 1) have demonstrated that an increased rate of C-2 H–D exchange of an azolium ring correlates with an increased susceptibility to hydrolysis. Also compare the relative rates of C-2 H–D exchange (D. S. Kemp and J. T. O'Brien, *J. Am. Chem. Soc.*, 1970, **92**, 2554) *vs.* the pK_a for hydrolysis (Y. Asahi and M. Nagaoka, *Chem. Pharm. Bull.*, 1971, **19**, 1017) of *N*-alkylbenzothiazolium *vs.* *N*-alkylthiazolium salts.

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