NMR ($CDCl_3$) δ 6.78 (1 H, s, aromatic H), 2.60 (3 H, s, CCH_3), 2.34 (3 H, s, CCH_3), and 2.17 (3 H, s, SCH_3); MS *m/e* 202 (M^+).

Reaction of 4-Methylsulfinyl-3,5-xylenol with Acetic Anhydride. A suspension of 4-methylsulfinyl-3,5-xylenol (**1**; 410 mg) in benzene (10 mL) was treated with an excess of acetic anhydride (0.5 mL) and refluxed with stirring for 48 h. Workup and purification as outlined for the acetyl chloride reaction afforded one major compound (R_f 0.33) which crystallized from hexane to give the 2,5-dienone **6** (41 mg): mp 110–112 °C; IR (Nujol) 1745, 1660, 1620 cm^{-1}; NMR ($CDCl_3$) δ 6.20 (2 H, s, dienone H), 2.18 (3 H, s, SCH_3), 2.04 (6 H, s, CCH_3), and 1.84 (3 H, s, OAc); MS *m/e* 226 (M^+). Crystallization of the minor compound (R_f 0.76) from hexane gave 2-acetoxy-4-methylthio-3,5-xylenol (**7**; 17 mg): mp 84–85 °C; IR (Nujol) 3310, 1738, and 1565 cm^{-1}; NMR ($CDCl_3$) δ 6.78 (1 H, s, aromatic H), 2.36 (3 H, s, CCH_3), 2.34 (3 H, s, OAc), 2.22 (3 H, s, CCH_3), and 2.16 (3 H, s, SCH_3); MS *m/e* 226 (M^+).

Reaction of 4-methylsulfinyl-3,5-xylenol (**1**) in a 2:1 mixture of acetic anhydride–acetic acid at 100 °C went to completion within an hour. The predominant product was the 2-acetoxy compound **7**, and a trace of the dienone **6** was also isolated.

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Registry No.—**1**, 22454-92-8; **3**, 67030-99-3; **4**, 88-04-0; **6**, 67031-00-9; **7**, 67031-01-0; 4-methylthio-3,5-xylenol, 7379-51-3.

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Model Studies of Thiamin Catalysis. Inductive Effects of Nitrogen-Bonded Substituents and Influence of Steric Inhibition of Resonance on Kinetic Carbon Acidities of Thiazolium Ions

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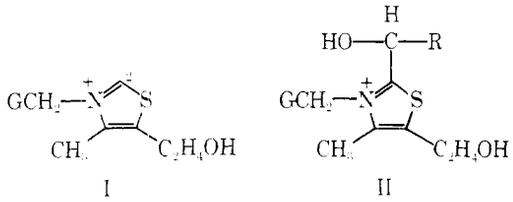
Thiazolium ions are important catalysts both in biological[1] and in chemical systems.[2] Thiamin or vitamin B_1 (I), for example, is involved in a number of transformations involving carbonyl compounds, such as the conversion of acetaldehyde to acetoin.[3] Similarly, other thiazolium salts are useful catalysts in the synthesis of acyloins.[2]



I

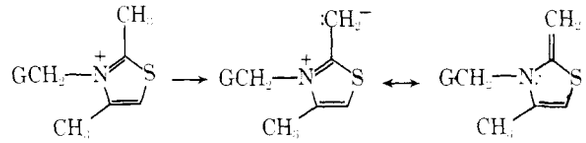
II

I, IIa, G = 4-amino-2-methylpyrimidinyl
IIb, G = H; R = CH_3

Key steps in the mechanism of acyloin formation include deprotonation of a thiazolium ion at position 2 to give an ylide which then adds to a carbonyl electrophile. Resultant intermediate II then is deprotonated at the newly formed side chain to give a second nucleophile, often called an "enamine". Reaction of this enamine with additional carbonyl compound followed by expulsion of ylide gives rise to acyloin product.

On a more detailed level, our current knowledge is very limited. Consideration of the reactivity of a series of substituted thiazolium ions at each step of the multistep sequences reveals that much remains to be learned.

We report results designed to clarify some aspects of this complex mechanism. We have measured the influence of substituents at an annular nitrogen atom on the rates of deprotonation of simple thiazolium ions (III) to produce an enamine (eq. 1). Our results provide an indication of how



III, G = H, C_6H_5, p-$O_2NC_6H_4$, CN (1)

sensitive side-chain deprotonation is to inductive effects of nitrogen-bonded substituents. A second aspects of our study deals with the magnitude of steric inhibition of resonance found when IIb (G = H, R = CH_3) is deprotonated at the 1-hydroxyethyl position.

Results and Discussion

Inductive Effects. Rates of deprotonation of 2,4-dimethylthiazolium ions (III) having groups G = H, C_6H_5, p-$O_2NC_6H_4$, and CN were obtained by studying hydrogen isotope exchange. Loss of a proton from the 2-methyl group to give a resonance stabilized conjugate base, eq 1, was catalyzed by acetate ion buffers in D_2O. Neither water nor deuterioxide compete significantly with acetate ion general base; pseudo-first-order rate constants for deprotonation, k_ψ, can be converted to second-order rate constants k_B reflecting acetate ion catalysis according to the equation

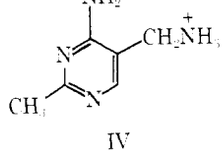
$$k_\psi = k_B[CH_3CO_2^-] \quad (2)$$

Examination of the results in Table I shows that k_B obtained in this way is essentially constant as the concentration of catalyst is varied by as much as tenfold.

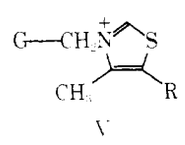
Comparison of the four k_B values reveals that substituents G, in spite of being removed from the thiazolium ring by a saturated carbon atom, have a significant influence on kinetic acidity. Comparing k_B values and using the value for G = H as a reference gives rise to relative rate constants of 1.0, 9.1, 27, and 187 for substituents G = H, C_6H_5, p-$O_2NC_6H_4$, and CN, respectively.

A linear free-energy correlation can be constructed between the logarithm of k_{rel} and pK_a values for substituted methylammonium ions, $GCH_2NH_3^+$,[4,5,8] having the same substituents. The slope of this correlation (correlation coefficient r = 0.962) is −0.40. Electron-withdrawing substituents promote the acidity of both the carbon and nitrogen acids. Naturally, effects are smaller in the case of the carbon acids where proton transfer is less complete. Although electron-withdrawing substituents destabilize both the positively charged carbon acid and the transition state, effects on transition-state energies are smaller because of extensive charge neutralization.

Using the pK_a (8.01) of methylammonium ion IV substituted with a pyrimidine ring as in thiamin and the free-energy



IV



V

Table I. Kinetic Results for Hydrogen–Deuterium Exchange at the 2-Methyl Group of 3-Substituted 2,4-Dimethylthiazolium Ions in Acetate-Buffered D_2O at 75.0 °C and 1.0 M Ionic Strength

substituent	registry no.	pD[a]	total buffer, M[b]	10^4k_ψ, s^{-1}	10^3k_B M^{-1} s^{-1}	k_{rel}
CH_3	29488-88-8	5.45	0.030	0.030	0.150	
		5.84	0.240	0.290	0.124	
					av 0.137 ± 0.013	1.0
$C_6H_5CH_2$	67145-81-7	5.10	0.500	2.76	1.13	
		5.13	0.080	0.49	1.23	
		5.20	0.350	2.22	1.16	
		5.79	0.120	1.43	1.44	
					av 1.24 ± 0.10	9.1
p-$O_2NC_6H_4CH_2$	67145-82-8	5.11	0.400	6.80	3.43	
		5.14	0.040	0.78	3.71	
		5.20	0.350	6.94	3.63	
		5.79	0.120	3.73	3.77	
					av 3.64 ± 0.11	27
$NCCH_2$	67145-83-9	4.33	0.060	0.246	29.4	
		5.09	0.100	12.7	25.9	
		5.09	0.154	18.7	24.9	
		5.09	0.200	21.4	22.1	
					av 25.6 ± 2.1	187

[a] Measured at 25 °C. [b] $pK_a = 5.12$.

Table II. Kinetic Results of Hydrogen–Deuterium Exchange at the 2 Position of 2,3,4-Trimethylthiazolium and 2-(1-Hydroxyethyl)-3,4-dimethyl-5-(2-hydroxyethyl)thiazolium Ions in Phosphate Buffered D_2O at 75.0 °C and 1 M Ionic Strength

compd	pD[a]	total buffer, M[b]	10^6k_ψ, s^{-1}	k, M^{-1} s^{-1}
III (G = H)	6.09	0.220	101	5.81×10^{-3} (DPO_4^{2-})
	7.17	0.040	162	(45) (OD^-)
	7.24	0.240	794	
	8.16	0.058	525	
IIb[c]	6.74	0.420	4.68	3.34×10^{-5} (DPO_4^{2-})
(G = H; R = CH_3)				
	7.03	0.203	3.22	2.4 (OD^-)
	7.12	0.300	5.56	
	7.17	0.403	8.86	
	7.72	0.360	14.7	
	8.19	0.320	20.9	

[a] At 25 °C. [b] pK_a 7.10. [c] Registry no.: 67145-84-0.

correlation ($\log k_{rel} = -0.40\ pK_a + 4.55$), it is possible to estimate that this substituent will increase reactivity by about a factor of 20 over that for G = H. The effect is similar to that produced by a nitrophenyl group. We expect that a similar correlation will apply to the kinetic acidities of thiazolium ions having hydroxyalkyl side chains (II).

Unfortunately, it is not possible to make an unequivocal comparison between the effects of substituents on ylide and on enamine formation. Two different values for the slope of a $\log k_{rel}$ vs. pK_a correlation for ylide formation can be derived from published data; both are the result of two point correlations. Thus, data for the lyate ion catalyzed dedeuteration of thiazolium ions V, where G is H and C_6H_5 (R = H), give a slope of −0.37,[12] while data for the detritiation of I and of V having phenyl as group G (R = CH_3) yield −0.80.[13] However on the assumption that both pairs belong to a single correlation, a three-point plot may be constructed using G = C_6H_5[14] as a common reference. The slope is −0.60 (r = 0.986). It would seem that ylide rather than enamine formation is more sensitive to substituent effects. Such a conclusion would be understandable in terms of a more product like transition state for the ylide reaction[15] with its associated greater amount of negative charge.

Inhibition of Resonance. By examining the reactivity of a series of 2-substituted-3-methylbenzothiazolium ions we demonstrated earlier that the rate of deprotonation of a 1-hydroxyethyl group is retarded due to steric inhibition of resonance in the transition state. Relative to a methyl group a 1-hydroxyethyl substituent is about 35 times less reactive toward either water or formate ion base.[16] In order to establish the magnitude of such inhibition in thiazolium ions having structures more like those of thiamin and its derivatives, the following experiments were performed.

The reactivity of III, G = H, was determined at 75.0 °C toward phosphate base. Under these more basic conditions deuterioxide ion provides a contribution to the rate of deprotonation along with buffer base. Pseudo-first-order rate constants are represented by the equation

$$k_\psi = k_B[DPO_4^{2-}] + k_{OD}[OD^-] \quad (3)$$

where a second term is present to reflect additional catalysis, k_{OD} being the second-order rate constant for lyate ion. However, the relative contribution of lyate ion to the rate is large only in the last run in Table II, where it is 44%. Consequently, the reported k_{OD} value should be regarded as approximate.

Similarly, deprotonation of IIb (G = H; R = CH_3), a structurally close relative of the biologically important thiamin derivative IIa,[1] was investigated using the same buffer. Kinetic data again may be dissected into component parts representing buffer and lyate ion catalysis (eq 3). This time the k_{OD} rate constant is likely to be estimated more closely because lyate ion catalysis is present at a significant

level in more runs, being 46% in the run at the highest pD.

Using the second-order rate constants given in Table II for both substrates and the appropriate concentrations of bases, it is possible with the aid of eq 3 to calculate a value for k_ψ. The calculated value differs from the observed value on the average by 4.2 and 8.7% in the case III and IIb, respectively.

Comparison of the second-order rate constants associated with phosphate ion general base for III and IIb (Table II) reveals that the thiazolium ion with the acidic methyl group is 174 times more reactive than the 1-hydroxyethyl ion. This value is five times larger (174 vs. 35)[16] than that we reported for benzothizolium ions reacting with water and formate ion bases.[16] The larger ratio found in the present study is due in part to the presence of the 5-(2-hydroxyethyl) group of IIb, which is absent from III. This electron-donating group decreases the reactivity of IIb, thereby increasing the magnitude of the rate constant ratio. A similar reactivity pattern is found for the two carbon acids toward lyate ion. But due to the uncertain value of k_{OD} for III, an accurate ratio cannot be calculated.

As is the case for benzothiazolium ions,[16] the primary reason for the diminished reactivity of the 1-hydroxyethyl chain is steric inhibition of resonance. Interaction between the hydroxy group of this chain with the substituent bonded to nitrogen prevents maximum orbital overlap, resulting in effective delocalization of the electrons from the reactive CH bond into the positively charged ring in the transition state. The unfavorable interaction leads to an increase in the energy barrier and a reduced rate.

Clearly a start has been made, but much yet remains to be done to develop our understanding of reactions catalyzed by thiazolium ions.

Experimental Section

Rates of hydrogen–deuterium exchange were determined by a previously employed NMR method on buffered solutions in D_2O.[16] Ionic strength was maintained at 1.0 M using KCl. In the case of fast runs on the cyanomethyl substrate, the NMR probe was cooled to about 5 °C before analysis in order to minimize continuing isotope exchange. Kinetic plots were constructed using the 2:4 group area ratio. The pD of solutions was measured at room temperature; owing to the slight temperature dependence of the dissociation constant of the buffers,[17] values are expected to be very similar to those at 75 °C, the reaction temperature. The pD was measured before and after each run; changes were <0.1 except in the slowest run for the cyanomethyl substrate, where a decrease of 0.16 was recorded. The initial value was used.

Equation 3 contains two unknowns, second-order rate constants k_B and k_{OD}, whose values are determined by treating the four (III) or six (IIb) values of k_ψ in Table II as a series of overdetermined simultaneous equations. Lyate ion concentration is calculated from a measured pD and $pK_w = 13.53$ (D_2O, 75 °C), while the concentration of DPO_4^{2-} is given by the product of the total phosphate buffer concentration and the term $K_a/([D] + K_a)$.

3-Methyl-[18] and 3-benzyl-2,4-dimethylthiazolium[18] salts were prepared by quaternization. 3-(4-Nitrobenzyl)-2,4-dimethylthiazolium bromide, mp 203–205 °C, was made by the method used to synthesize the chloride.[19] Anal. Calcd for $C_{11}H_{11}BrN_2O_2S$: C, 43.78; H, 3.98; H, 8.51. Found: C, 43.84; H, 3.99; N, 8.45. Similarly, the 3-cyanomethyl salt was prepared from 2,4-dimethylthiazole and cyanomethyl chloride; it was isolated as the perchlorate; mp 225–227 °C dec. Anal. Calcd for $C_7H_9ClN_2O_4S$: C, 33.27; H, 3.59; N, 11.09. Found: C, 33.47; H, 3.63; N, 10.95. 2-(1-Hydroxyethyl)-3,4-dimethyl-5-(2-hydroxyethyl)thiazolium iodide was made from acetaldehyde and the 2-unsubstituted thiazolium iodide[20] by the method used to prepare 2-(1-hydroxyethyl)thiamin.[21] The yield of crude product was 64%; repeated recrystallization from methanol–ethyl acetate gave pure product, mp 106–107 °C (lit.[22] mp 109°).

pK_a of 2-Methyl-4-amino-5-(aminomethyl)pyrimidine Dihydrochloride. A 2.00×10^{-3} M solution of the title compound (Aldrich) was titrated potentiometrically with 0.0467 M KOH at 25.7 °C using a radiometer TTT-1C titrator. Data were treated according to the method of Albert Serjeant;[23] although overlap is minor, the data were analyzed on the assumption that the two ionization steps do overlap. No correction was applied to reflect changing ionic strength; corrections would modify pK_a values by ≤0.1. Five determinations gave pK_1 (ring) 4.85 and pK_2 (side chain) 8.01. Literature values include 7.1,[24] 8.4,[6] and 8.6.[7]

Control Runs. In order to determine whether D_2O might catalyze hydrogen exchange the 3-methyl and 3-benzyl substrates were heated for 127 h in 0.1 M DCl (ionic strength 1.0 M) at 75 °C. Approximately 2.5 and 7.7% deuteration took place at the 2-methyl group of each, respectively. This sets as upper limits to the rate constants values of 5.6×10^{-8} and 1.8×10^{-7} s^{-1}, respectively. Hence, catalysis by D_2O does not compete significantly with that by acetate ion.

Control runs on the 3-(*p*-nitrobenzyl) and 3-(cyanomethyl) substrates using acetate buffer in H_2O showed no evidence (NMR) of degradation after 12 half-lives for the former and after 3 half-lives for the latter. Some decomposition of the cyanomethyl compound was evident after heating for a period corresponding to 8 half-lives; new peaks appeared at higher field.

Samples of IIb (G = H; R = CH_3) degrade on heating in phosphate buffer. Early studies using low concentrations of buffer showed that the pD of reaction mixtures decreased substantially with time; therefore, kinetic runs were discarded. The use of higher buffer concentrations minimized the drift in pD. A sample in phosphate-buffered H_2O gave some evidence (NMR) of substrate decomposition after a period of heating at 75 °C, which corresponds to about 2.3 half-lives for isotope exchange; considerable starting material remained after about 6 half-lives. Some of the NMR signals which appear in the sample in H_2O are not observed in D_2O, suggesting H–D exchange. Decomposition products were not identified.

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Registry No.—3-(4-Nitrobenzyl)-2,4-dimethylthiazolium bromide, 67145-85-1; 3-cyanomethyl-2,4-dimethylthiazolium perchlorate, 67145-86-2; 2-(1-hydroxyethyl)-3,4-dimethyl-5-(2-hydroxyethyl)-thiazolium iodide, 52084-19-2; 2-methyl-4-amino-5-(aminomethyl)-pyrimidine dihydrochloride, 874-43-1; 2,4-dimethylthiazole, 541-58-2; cyanomethyl chloride, 107-14-2; acetaldehyde, 75-07-0; 3,4-dimethyl-5-(2-hydroxyethyl)thiazolium iodide, 16311-69-6; deuterium, 7782-39-0; thiamin, 59-43-8.

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