Fundamental Studies on Models for Thiamine. Generation of Ylides of Oxazolium, Imidazolium, and Thiazolium Ions by Decarboxylation. Applications to the Structure of the Thiamine Ylide[1]

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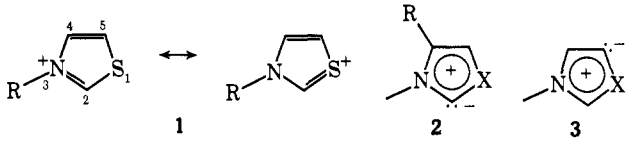
Abstract: Decarboxylation of thiazolium, oxazolium, and imidazolium carboxylates has been used as a technique for generation of heterocyclic ylides in order to evaluate the effect of an adjacent sulfur atom on ylide stability. The data suggest that both 2- and 5-acids decarboxylate through their zwitterionic tautomers. Studies on N-methylated azolium-5-carboxylates indicate that the 5-ylides are generated at approximate relative rates of $10^{5.4}$: $10^{8.0}$:1 for oxazolium, thiazolium, and imidazolium rings. Potential acidities in the ground state would lead to predicted rates which are similar for the thiazolium and imidazolium rings. The large difference between the two is therefore a transition state effect and must reflect the special bonding properties of sulfur in an azolium ring.

The fundamental structural reasons for the unique functions of the thiazolium ion (**1**) as the active part of the vitamin, thiamine, are still not clear. The role of the sulfur atom has been a subject of considerable discussion,[3] and this research provides further data toward understanding that problem.

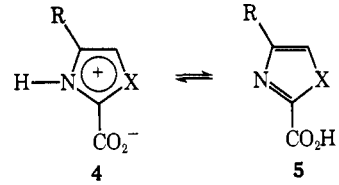
Our work on the rate of $^-$OD-catalyzed generation of 2-ylides (**2**, R = CH_3) indicates that the thiazolium ylide (**2**, X = S) is stabilized beyond the extent expected from the inductive electronic effects of the adjacent heteroatoms alone.[4] One possible reason may be delocalization, possibly involving d–σ overlap,[5] of the unshared pair of electrons at the 2 position toward



1 **2** **3**

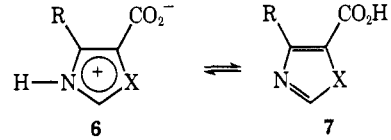
sulfur; this is not possible for X = nitrogen or oxygen. Recent work supports the view that the sulfur atom can expand its valence shell of electrons[5] beyond an octet, as in SF_6.[6,7]

If such stabilization is present in **2**, it should be quite useful to examine the rates of formation of **3**. In **3**, the unshared pair of electrons at the 5 carbon is adjacent to only one heteroatom, X. Therefore, interpretation of results for generation of **3** will not be complicated by the presence of the other heteroatom, nitrogen, as in **2**. However, since the 5-ylide, **3**, is stabilized by only one adjacent heteroatom, **3** would be expected to be much less stable than **2**. In fact, **3** cannot be generated by base-effected removal of a 5-hydrogen from **1**, because **1** is too unstable toward ring opening involving nucleophilic attack by $^-$OH at the 2 position.[8] Therefore, we have used decarboxylation of azolium carboxylates (**4**–**8**) as a means of generating ylides. From previous research on decarboxylations,[9] one would expect that the decarboxylation of the zwitterionic compounds, **4**, **6**, and **8**, would produce ylides and we have therefore used this technique to generate **3**. Some



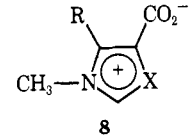
4 **5**

a, X = NCH_3; R = H
b, X = S; R = CH_3



6 **7**

a, X = NH; R = CH_3
b, X = S; R = CH_3
c, X = O; R = CH_3



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a, X = NCH_3; R = CH_3
b, X = S; R = CH_3
c, X = O; R = CH_3

(1) Research supported by Grant AM-12743 from the Institute of Arthritis and Metabolic Diseases, U. S. Public Health Service, and an Alfred P. Sloan Research Fellowship to P. Haake.
(2) Wesleyan University.
(3) R. Breslow, *J. Amer. Chem. Soc.*, 79 1762 (1957); *Ann. N. Y. Acad. Sci.*, **98**, 445 (1962).
(4) P. Haake, L. P. Bausher, and W. B. Miller, *J. Amer. Chem. Soc.*, **91**, 1113 (1969).
(5) (a) P. Haake and W. B. Miller, *ibid.*, **85**, 4044 (1963); (b) R. A. Olofson, J. M. Landesberg, K. N. Houk, and J. S. Michelman, *ibid.*, **88**, 4265 (1966), and preceding papers.
(6) K. A. R. Mitchell, *Chem. Rev.*, **69**. 157 (1969).
(7) K. A. R. Mitchell, *J. Chem. Soc. A*, 2676 (1968).
(8) P. Haake and J. Duclos, *Tetrahedron Lett.*, 461 (1970).
(9) (a) B. R. Brown, *Quart. Rev., Chem. Soc.*, **5**, 131 (1951); (b) P. Haake and J. Mantecon, *J. Amer. Chem. Soc.*, **86**, 5230 (1964).

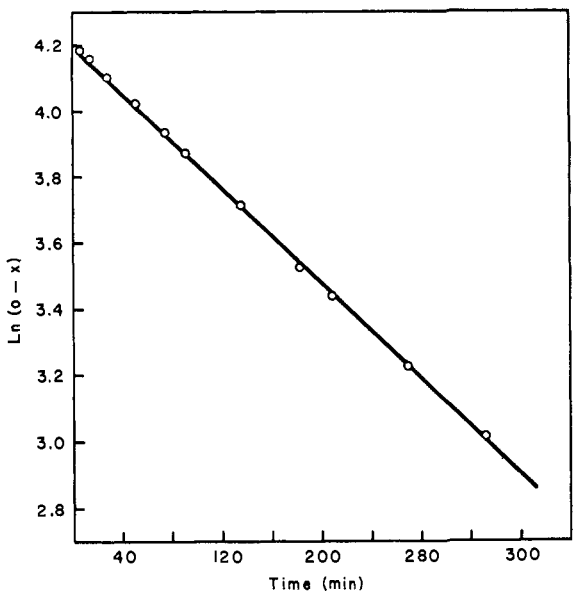


Figure 1. Decarboxylation of 4-methyloxazole-5-carboxylic acid at 185.4°.

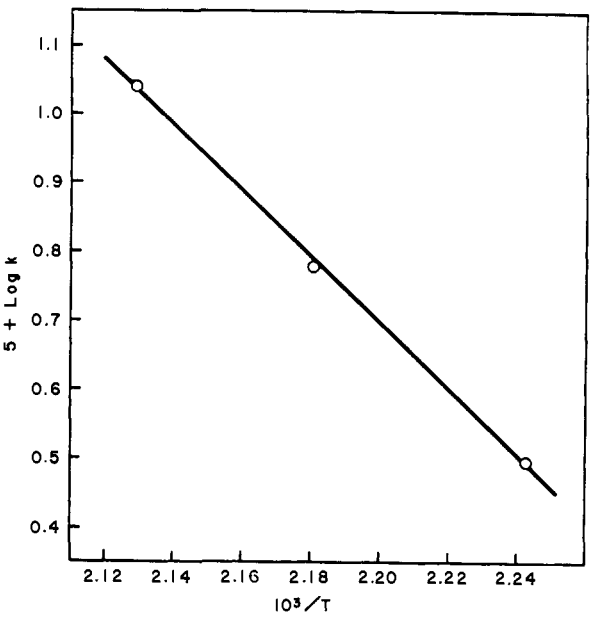


Figure 2. Arrhenius plot for 4-methyloxazole-5-carboxylic acid.

decarboxylations of thiazole acids have been studied,[10] and a number of other heterocyclic decarboxylations have been reported.[9,11-13]

Experimental Section

Materials. Ethylene glycol (Matheson Coleman and Bell, bp 196–198°) was dried over molecular sieves (16 mesh). Eastman synthetic grade quinoline was distilled before use. 2,6-Lutidine (Matheson Coleman and Bell 99%) was dried over BaO and distilled before use. *N,N*-Dimethylaniline (monofree, Eastman Kodak, mp 1.5–2.5°) was distilled before use.

Rate Measurements. The apparatus described by Haake and Mantecon[9b] was utilized. In a typical experiment 0.3–1.0 mmole of the compound was dissolved in 20 ml of ethylene glycol. The solvent contained an equivalent amount of amine (Table I) if an acid salt was used rather than a zwitterion. The solution was placed in the apparatus described above, and a carefully regulated flow of nitrogen, prepurified by passage through Drierite and Ascarite, was swept through the system. The flask was lowered into a constant temperature bath, and the amount of CO_2 evolved was measured by weighing alternately the Ascarite absorption tubes to the nearest 0.1 mg. All compounds dissolved as thermal equilibrium was attained. The bath temperature was kept constant to ±0.1°.

Calculations. The first-order rate constants were calculated graphically from the equation, $2.3 \log W_\infty/(W_\infty - W_t) = kt$, where W_∞ = calculated weight of CO_2 produced at 100% reaction and W_t = weight of CO_2 evolved at time, t. After the reacting solution reached bath temperature (10–20 min), straight lines were obtained to more than 65% reaction in most cases. Very slow decarboxylations tended to be nonlinear after 50% reaction.

A typical graphical determination of a rate constant is shown in Figure 1. The initial curvature of the line corresponds to the time required for thermal equilibration.

Activation parameters were calculated[14] from the Arrhenius energy of activation which was calculated from a least-squares plot of log k *vs.* $1/T$. A typical plot is shown in Figure 2.

Preparation of Compounds. The preparation of the following compounds was described in an earlier paper:[15] 1-methylimidazole-2-carboxylic acid (**5a**), 4-methylthiazole-2-carboxylic acid (**5b**), 4-methylimidazole-5-carboxylic acid (**7a**), 4-methylthiazole-5-carboxylic acid (**7b**), 4-methyloxazole-5-carboxylic acid (**7c**).

Table I. Rate Constants for Decarboxylation of Azole Acids in Ethylene Glycol

Compound	% R^a	Temp, °C	$10^5 k_{obsd}$, sec^{-1}
6b ⇄ **7b**	89	172.4	21.9
	85	172.5	19.7
	56	148.9	2.46
4b ⇄ **5b**	84	59.9	56.8
8b[b]	49	105.7	6.43
	91	115.2	21.3
	89	127.4	69.7
6a ⇄ **7a**	39	172.9	3.16
4a ⇄ **5a**	50	59.9	4.37
8a	93	191.3	81.1
	93	182.6	33.6
	88	166.4	8.77
6c ⇄ **7c**	57	172.7	3.13
	69	185.4	6.0
	73	196.6	11.0
8c[c]	65	84.9	49[d]
	68	50.3	8.8[e]
	44	77.0	20[f]
	67	77.0	33[d]
		77.0	56[g]

[a] Per cent reaction over which rate was followed. [b] Generated **8b** in solution from the *p*-toluenesulfonate salt of protonated **8b**; solvent contained 1 equiv of quinoline. [c] Generated **8c** in solution from the *p*-toluenesulfonate salt of protonated **8c** by an added amine: footnotes *d–g*. Rate constants are approximate. [d] One equivalent of quinoline in the solvent. [e] Two-thirds equivalent of quinoline in the solvent. [f] One equivalent of 2,6-lutidine in the solvent. [g] One equivalent of *N,N*-dimethylaniline in the solvent.

Ethyl 1,4-Dimethylimidazole-5-carboxylate. We used a procedure employed by Pyman[16] for the methyl analog. Ethyl 4-methylimidazole-5-carboxylate[17] (25 g) and dimethyl sulfate (25 g) were heated together at 100° for 30–40 min. Solid potas-

(10) (a) H. Schenkel and M. Schenkel-Rudin, *Helv. Chim. Acta*, **31**, 514, 924 (1948); (b) H. Schenkel and R. Mory, *ibid.*, **33**, 16 (1950).
(11) (a) N. H. Cantwell and E. V. Brown, *J. Amer. Chem. Soc.*, **75**, 4466 (1953); (b) C. Tanaka, *Yakugaku Zasshi*, **85**, 193 (1965).
(12) G. J. Litchfield and G. Shaw, *Chem. Commun.*, 563 (1965).
(13) L. W. Clark, *J. Phys. Chem.*, **69**, 2277 (1965), and previous papers in the series.
(14) K. J. Laidler, "Chemical Kinetics," McGraw-Hill, New York, N. Y., 1950, p 73.
(15) P. Haake and L. P. Bausher, *J. Phys. Chem.*, **72**, 2213 (1968).
(16) W. Hubball and F. L. Pyman, *J. Chem. Soc.*, **21** (1928).
(17) Synthesized by the method of H. Böhme and H. Schneider, *Chem. Ber.*, **91**, 988 (1958). The compound gave an nmr spectrum which was consistent with the structure.

sium carbonate was added to bring the solution to pH 9 and the mixture was extracted three times with chloroform. The combined extracts were washed twice with aqueous potassium carbonate, dried, and concentrated to a dark red oil. Fractional distillation with a Vigreaux column gave 8.8 g of product, bp 75° (0.22 Torr), that solidified upon standing: nmr ($CDCl_3$): τ 2.6 (singlet, 1 H), 5.54–5.90 (quartet, 2 H), 6.2 (singlet, 3 H), 7.56 (singlet, 3 H), 8.55–8.78 (triplet, 3 H); ir (neat): 3.13, 3.29, 3.32, 5.85, 6.42, 6.61, 6.76, 6.82, 6.91, 7.10, 7.21, 7.27, 7.32, 7.42, 7.65, 7.82, 8.28, 8.55, 8.85–9.05, 9.51, 9.85, 10.3, 11.56, 11.93, and 12.96 μ. *Anal.* Calcd for $C_8H_{12}N_2O_2$: C, 57.13; H, 7.19. Found: C, 56.98; H, 7.26.

1,3,4-Trimethyl-5-carbethoxyimidazolium Iodide. Ethyl 1,4-dimethylimidazole-5-carboxylate (5 g) and 50 ml of methyl iodide were refluxed overnight. Removal of the methyl iodide left a white, crystalline product which was recrystallized from ethanol–ether to give 9.1 g of crystals: mp 104–107°; nmr (D_2O): τ 0.99 (singlet, 1 H), 5.28–5.65 (quartet, 2 H), 5.86 (singlet, 3 H), 6.07 (singlet, 3 H), 7.32 (singlet, 3 H), 8.41–8.65 (triplet, 3 H); ir (Nujol): 3.38, 3.44, 5.80, 6.18, 6.31, 6.79–6.86, 7.04, 7.25, 7.66, 8.20, 8.43, 8.86, 9.0, 9.18, 9.64, 9.88, 11.47, 11.68, 12.1, 12.3, 13.07, and 13.9 μ; uv (H_2O): λ_{max} 226 mμ. *Anal.* Calcd for $C_9H_{15}N_2O_2I$: C, 34.85; H, 4.88. Found: C, 35.11; H, 5.06.

1,3,4-Trimethylimidazolium-5-carboxylate, (8a). 1,3,4-Trimethyl-5-carbethoxyimidazolium iodide (3.45 mmoles) was added to 12 ml of 0.287 *M* sodium hydroxide (3.45 mmoles). The solution was stirred at room temperature for 1 hr and then washed through a Dowex 1-X8 (50–100 mesh) ion-exchange column in the chloride form. The eluate was lyophilized to dryness, leaving a dry, amorphous, white powder that contained the imidazolium carboxylate betaine and sodium chloride. The per cent chloride present was determined by argentometric titration and indicated that the powder contained 27.4% sodium chloride: nmr (D_2O): τ 1.29 (singlet, 1 H), 5.95 (singlet, 3 H), 6.14 (singlet, 3 H), 7.46 (singlet, 3 H); ir (nujol): 2.90, 3.40, 4.60, 6.02, 6.16, 6.26, 6.4, 6.87, 7.17, 7.3, 7.40, 7.60, 8.14, 8.50, 9.13, 9.22, 9.58, 11.46, 11.74, 12.56, and 13.90 μ.

3,4-Dimethylthiazolium-5-carboxylic Acid *p*-Toluenesulfonate (*p*-Toluenesulfonate Salt of Protonated 8b). 4-Methylthiazole-5-carboxylic acid[15] (1 g) and 10 ml of methyl *p*-toluenesulfonate were heated together at 120° for 2 hr or until all material had dissolved. The hot solution was quickly filtered into a flask containing acetone. Crystals appeared immediately and were filtered and washed with acetone–ether solution: mp 178–182°; nmr (D_2O): τ 0.10 (singlet, 1 H), 2.23–2.72 (quartet, 4 H), 5.88 (singlet, 3 H), 7.25 (singlet, 3 H), 7.63 (singlet, 3 H); ir (Nujol): 2.98, 3.4, 5.2, 5.85, 6.26, 6.85, 7.28, 7.80, 8.24, 8.55, 8.95, 9.74, 9.95, 11.6, 12.22, 13.12, 13.87, and 14.76 μ; uv (H_2O): λ_{max} 225 mμ. *Anal:* Calcd for $C_{13}H_{13}NS_2O_5 \cdot 0.5H_2O$: C, 46.20; H, 4.77. Found: C, 46.57; H, 5.04.

3,4-Dimethyloxazolium-5-carboxylic Acid *p*-Toluenesulfonate (*p*-Toluenesulfonate Salt of Protonated 8c). 4-Methyloxazole-5-carboxylic acid[15] (1 g) and 10 ml of methyl *p*-toluenesulfonate were heated together at 100° until all of the solid dissolved. The hot solution was poured into a flask containing acetone, and the acid salt precipitated immediately. The solid was filtered and recrystallized from ethanol–ether, mp 167.5–169°. Prolonged contact with polar solvents appeared to cause decomposition: nmr (D_2O): τ 0.17 (singlet, 1 H), 2.23–2.72 (quartet, 4 H), 6.05 (singlet, 3 H), 7.45 (singlet, 3 H), 7.62 (singlet, 3 H); ir (nujol): 3.21, 3.35, 3.42, 4.17, 5.3, 5.82, 6.0, 6.43, 6.86, 7.20, 7.28, 7.67, 7.82, 8.16, 8.32, 8.48, 8.53, 8.78, 8.9, 9.05, 9.38, 9.70, 9.95, 10.45, 10.72, 11.15, 11.60, 12.12, 12.50, 13.0, 13.13, 14.04, 14.64, and 14.73 μ. *Anal.* Calcd for $C_{13}H_{15}NO_6S$: C, 49.80; H, 4.84. Found: C, 50.02; H, 5.01.

Results

Because of the need for high temperatures in some decarboxylations, ethylene glycol was used as the solvent.[9b] The observed rate constants are given in Table I. Since **8a** could not be obtained in pure form after a number of attempts, the decarboxylation was carried out with a 1:1 mixture of NaCl and **8a** (see Experimental Section). The presence of NaCl should have little effect on the rates. We generated **8b** and **8c** in solution from the *p*-toluenesulfonate salts of the protonated forms using an amine in the solvent. The protonated forms of **8b** and **8c** are strong acids[15] so proton transfer should be essentially complete in ethylene glycol. However, the oxazole compound **8c** gave some problems, for a deep red color developed in the solution as decarboxylation proceeded. This is probably a result of ring opening followed by condensation reactions. The oxazolium ring is very susceptible to base-effected ring opening.[8] Consequently, we carried out a series of experiments using a variety of amines. Although there is variation in rate from one amine to another, the rates are sufficiently accurate so that the rate of decarboxylation of **8c** is known fairly well. The rate constant of 56 $\times 10^{-5}$ sec^{-1} at 77.0° in the presence of *N,N*-dimethylaniline is a representative value.

The primary concern in this research was relative rates of decarboxylation, particularly of **8a**, **8b**, and **8c**. The widely different temperatures required for measurable rates necessitated extrapolation of rate data to temperatures where measurements were impossible. The activation parameters in Table II reflect the results of plotting log k *vs.* $1/T$ and these data were used to obtain extrapolated rate constants. In Table III the extrapolated rate constants for **8a** and **8b** are compared with the representative rate constant for decarboxylation of **8c**.

Table II. Activation Parameters for Azole Decarboxylations

Compound	E_a[a]	$\Delta H^{\ddagger}$[a]	$\Delta G^{\ddagger}$[a]	$\Delta S^{\ddagger}$[b]	Temp, °C
7b	33.9	33.0	33.9	−2.1	172.4
7c	21.7	20.8	36.1	−33.4	185.4
8b[c]	33.3	32.5	29.6	+7.5	115.2
8a	36.3	35.4	34.2	+2.6	182.6

[a] Units of kcal/mole. [b] Units of cal/mole deg. [c] Generated from the *p*-toluenesulfonate salt of protonated **8b**.

Table III. Relative Rates of Decarboxylation

Compound	Temp, °C	10^5k (sec^{-1})	Rel k (59.9°)	Rel k (77.0°)
4a	59.9	4.37[a]	$10^{5.5}$	
8a	59.9	1.3×10^{-5} [b]	1	
8a	77.0	2.0×10^{-4} [b]		1
8b	77.0	0.2[b]		$10^{3.0}$
8c	77.0	55.5[a]		$10^{5.4}$

[a] Measured rate constants (Table I). [b] Extrapolated (Table II).

Discussion

Azole-2-carboxylic Acids (4 ⇄ 5). A comparison of the rate of decarboxylation of 4-methylthiazole-2-carboxylic acid in ethylene glycol with those of thiazole-2-carboxylic acid in quinoline and dichloroacetic acid[10] (Table IV) supports the hypothesis that decarboxylation of thiazole-2-carboxylic acids proceeds through zwitterions (**4b**). The fastest rate occurs in the neutral solvent, ethylene glycol, which should contain a higher concentration of the zwitterionic form. The reaction rate of the unsubstituted acid in ethylene glycol might be expected to be slightly faster than the 4-methyl acid because the 4-methyl group's electron donation would be expected to inhibit decarboxylation.

Table IV. Observed Rates of Decarboxylation of Thiazole-2-carboxylic Acids in Different Solvents at 59.9°

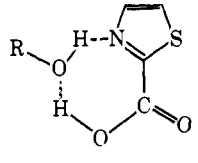
Compound	Solvent	$k \times 10^5$ (sec^{-1})
4-Methylthiazole-2-carboxylic acid	Ethylene glycol	56.8
Thiazole-2-carboxylic acid	Quinoline	11.5[a,b]
	Dichloroacetic acid	3.8[a,b]

[a] H. Schenkel and M. Schenkel-Rudin, *Helv. Chim. Acta*, **31**, 924 (1948). [b] The rate constants at 59.9° were calculated from the data of Schenkel and Schenkel-Rudin according to $k_1 = k_2 \exp(E_a \Delta T / RT_1T_2)$.

Tanaka[11b] has concluded that decarboxylation of oxazole-2-carboxylic acids proceeds through the zwitterionic form (**4**, X = O). Solvent change to lower dielectric constant and addition of an amine lower the rate.

Both the oxazole and thiazole acids are predominantly in the uncharged state, **5**.[15] However, the imidazole-2-carboxylic acid is predominantly a zwitterion, **4**.[15] Therefore, this acid should certainly decarboxylate through the zwitterion, **4**; in the zwitterionic form, electron withdrawal by the ring is large and electron density on the CO_2 is large—both effects will promote decarboxylation.[9]

However, the predominance of the thiazole-2-carboxylic acid in form **5** may make it difficult to distinguish involvement of a true zwitterion from proton transfer during decarboxylation of a hydrogen-bonded form, *e.g.*, **9**. We cannot distinguish these alternatives from the present data.



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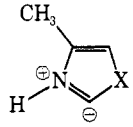

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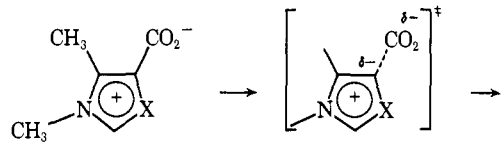
Azole-5-carboxylic Acids. The 5-carboxylic acids can also exist as zwitterions (**6**) or in uncharged form (**7**). The data in Table I provide strong evidence for decarboxylation through the zwitterions, **6**.[18] (1) Decarboxylations of the N-methylated compounds, **8b** and **8c**, are much faster than decarboxylations of the thiazole and oxazole-5-carboxylic acids because of the small fraction of these acids in forms **6b** and **6c** through which decarboxylation proceeds. (2) The *N*-methylimidazolium betaine (**8a**) decarboxylates at nearly the same rate as the imidazole-5-carboxylic acid, which is known to exist predominantly in the zwitterionic form, **6a**.[15] (3) The decarboxylations of the *N*-methylthiazolium betaine (**8b**), and the thiazole acid, **7b**, have similar activation energies. The rest of the barrier for decarboxylation of **7b** is probably the entropy barrier associated with **7b** → **6b**. Since **6b** is highly polar it will tend to order solvent much more than **7b**. The oxazole-5-carboxylic acid (**7c**) decomposes with a considerably lower E_a (or $\Delta H^{\pm}$) than the other compounds, although $\Delta G^{\pm}$ is slightly higher than for **7b**. The oxazole-5-carboxylic acid appears to exist with considerably less zwitterion present at equilibrium than the thiazole-5-carboxylic acid. There is therefore a greater entropy barrier for **7c** than for **7b**, but, as in **8c**, the zwitterion decarboxylates with a low activation barrier due to electron withdrawal by O and N^+ in the ring.[20]

Relative Stabilities of Ylides. This paper is based on the hypothesis that decarboxylation of **8** (or **6**) generates the ylide **3**. There seems to be little doubt that this is correct. The decarboxylations appear to be unimolecular based on the kinetics and the entropy of activation (Table II). Since it is the zwitterion, not the protonated acid, that is reactive for decarboxylation, ylide should be formed. In decarboxylations which proceed less readily, a carbanion appears to be generated.[9] With the stabilization provided by the azolium rings, ylides certainly should be formed in decarboxylations. For all these reasons, the relative rates in Table III do appear to represent relative rates of the reaction



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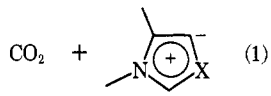

(1)

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2-Ylides Compared to 5-Ylides. Since all the imidazoles exist predominantly in zwitterionic forms,[15,19] the absolute rates for **4a**, **6a**, and **8a** (Table I) demonstrate the greater stabilization of 2-ylides (**2**) than of 5-ylides (**3**). There is over a 100° difference in temperature required for similar rates of generation of **2** and **3**. Extrapolation using the activation energy for **8a** yields (for 59.9°) k (**8a**) = 1.3×10^{-10} sec^{-1} (Table III). Comparison with data for **4a** indicates that the 2-CO_2^- compound decarboxylates 3.4×10^5 times faster than the 5-CO_2^- compound (**8a**). Since the rate for **6a** is considerably slower than for **8a**, the comparison between the analogous acids, **4a** and **6a**, is approximately 10^6.

Relative Stabilities of 5-Ylides. Table III also gives the relative rates observed for the closely analogous acids **8a**, **8b**, and **8c**. We are mainly concerned with the relation of these relative rates to the stability of the azolium ylides and the question of why the thiazolium acid decarboxylates 10^3 faster than the imidazolium acid.

One approach to this question involves the use of ^{13}C–H coupling constants to estimate the potential acidity of the ground state. This argument was elaborated in our previous paper.[4] Recent work demonstrates that our argument is correct. Streitwieser, *et al.*,[21] have recently found that the kinetic acidity of C–H bonds in hydrocarbons is directly related to the magnitude of the C–H coupling. Although covering a smaller range of structures, Closs and Larrabee[22] had

(18) This conclusion conflicts with ref 10 but appears confirmed by the magnitude of the tautomeric equilibrium constants which we determine.[19]

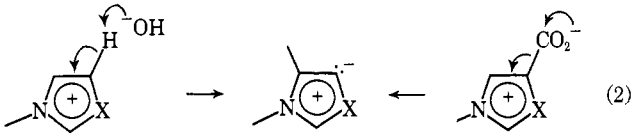
(19) P. Haake, J. P. McNeal, and L. P. Bausher, unpublished results.

(20) This effect also is seen in the rapid proton exchange of oxazolium ions.[4]

(21) A. Streitwieser, R. A. Caldwell, and W. R. Young, *J. Amer. Chem. Soc.*, **91**, 529 (1969).

(22) G. L. Closs and R. B Larrabee, *Tetrahedron Lett.*, 287 (1965).

earlier come to the same conclusion. It therefore appears to be true that C–H couplings can be used to estimate the potential acidity of the C_5–H bond in azolium ions. Although we have studied decarboxylations, the fact that 5-ylides are generated either by decarboxylation or by base-catalyzed proton abstraction (eq 2) enables us to estimate expected rates of decarboxylation from ^{13}C–H couplings.



5-ylide (2)

The ^{13}C–H couplings at the 5 position are: oxazolium ion, 224 Hz; thiazolium ion, 202 Hz; and imidazolium ion, 201 Hz.[4] Since the thiazolium and imidazolium couplings are nearly the same, the bonds to C_5 in **8a** and **8b** appear to have similar polarization in the ground state. This then suggests that the much greater rate for the thiazolium compound (Table III) is due to some other factor than inherent weakness of the bonds to C_5.

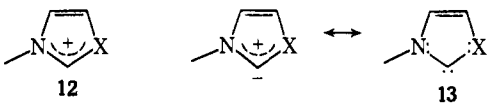
Consideration of electronegativity supports this conclusion. The electronegativity of the adjacent heteroatom should be an important factor in rates of decarboxylation, since the rates of many decarboxylations seem to be dependent on how well the electron pair, which is released as CO_2 leaves, can be accommodated in the intermediate.[9] The greater electronegativity of N compared to S would lead one to expect a greater rate for **8a** than for **8b**. The fact that the reverse is true indicates greater complexity in the factors that determine the $\Delta G^{\pm}$.

Ylides are high energy intermediates. Although rates only reflect the energy difference between ground state and transition state, this appears to be a case where **3** is sufficiently close to the structure of the transition state for decarboxylation so that the ylide can be used as a model for the transition state.[23]

In our previous paper on proton exchange at the 2 position, the relative rates of abstraction of H^+ by HO^- were similar to the relative rates observed in this study of decarboxylation at the 2 position. This similarity appears quite significant. Bond lengths in thiamine[24] support a picture of the π system of **8** as indicated in **1** and represented by **12**.

(23) G. S. Hammond, *J. Amer. Chem. Soc*, 77, 334 (1955).

(24) J. Kraut and H. J. Reed, *Acta Crystallogr.*, **15**, 747 (1962); J. Petcher and M. Sax, *Science*, **154**, 1331 (1966); I. M. Karle and K. Britts, *Acta Crystallogr.*, 20, 118 (1966).



12 **13**

The 4–5 bond length is 1.32 Å as expected for a double bond, and the 1–5 bond is considerably longer than the 1–2 bond (1.75 Å *vs.* 1.68 Å). Molecular orbital calculations also support **12** as the best representation of the azolium structure. Self-consistent calculations result in a very high π bond order for the 4–5 bond and low π bond orders for the 1–5 and 3–4 bonds regardless of the input parameters.[25]

The relative rates of exchange observed for 2-hydrogens could have been ascribed to a special effect due to the incorporation of the 2-carbon in the delocalized diheteroallylic cation spanning the 1, 2, and 3 positions. In fact, several papers have ascribed the stability of 2-ylides to a carbenoid structure (**13**). *It is impossible to write a carbenoid structure at the 5 position.* The relative rates of decarboxylation at the 5 position therefore demonstrate that the rate of generation of azolium ylides is accelerated by the presence of a sulfur atom, the 2 position is not unique, and carbenoid structures are not critical to the rapid generation of thiazolium ylides compared to imidazolium ylides.

There appear to be two likely sources for the stability of thiazolium ylides, and these are discussed with eq 1 as a model. (1) Comparing the imidazolium and thiazolium cases, $-\Delta G^{\pm} = \Delta G(\mathbf{8}) - \Delta G(\text{ylide})$. The $\Delta\Delta G^{\pm}$ between the thiazolium and imidazolium decarboxylations can then be partially due to ylide stabilization by the sulfur atom (d–σ overlap) as considered in our previous paper.[4] The electronic energy of the free pair of carbon electrons in the ylide (**9**) will clearly be very dependent on any possibility for delocalization. (2) $\Delta G^{\pm}$ will be very dependent on the total $\Delta E(\pi) = E(\pi, \mathbf{8}) - E(\pi, \text{ylide})$; that is, $\Delta G^{\pm}$ will depend on the total change in π energy of the heterocycle as the ylide is generated. The increase in electron density at the carbon where the free pair is generated will greatly perturb π bonding in the heteroaromatic system and presumably lower the total π energy. The presence of the sulfur atom in thiazolium ions may enable mixing in of d orbitals so that π bonding remains strong in thiazolium ylides, but in imidazolium ylides the adjacent $N^{\delta+}$ and C^- atoms may have such poor ($2p\pi$–$2p\pi$) overlap that there is considerable loss of π bond energy as the ylide is formed.

(25) P. Haake, unpublished data.