Determination of Binding Constants. A typical experiment would consist of adding 10 separate 5-μL aliquots of a 100 mM solution of **1** (or **2a-c** or **3**) in DMSO-d_6 to 500 μL of a 5 mM solution of GMP free acid in DMSO-d_6 and recording the chemical shift changes in the guanine imino and amino protons. Data reduction for compounds **1** and **2a-c** was then effected by using the least-squares NMR curve fitting program of Whitlock.[24] As this program provides no built-in error analysis function, errors were estimated by carring out a "dummy" calculation on the extreme range of experimental values obtained from two separate (and independent) titrations. Unless otherwise indicated, the reported values are considered to be accurate to within ±15%. In the case of **3**, data reduction was effected by using a standard Scatchard plot.[22,23] Now, however, because of the low value involved, the errors are considered to be significantly larger, being on the order of 40%.

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Registry No. **1**, 130798-30-0; **1**·GMP, 130798-36-6; **2a**, 130798-31-1; **2a**·$^1/_2$GMP, 130798-35-5; **2b**, 130798-32-2; **2**, 130798-33-3; **3**, 130798-34-4; **4**, 71-30-7; **5a**, 130798-15-1; **5b**, 130798-16-2; **5c**, 130798-17-3; **6a**, 130798-18-4; **6b**, 130798-19-5; **6c**, 130798-20-8; **7a**, 130798-21-9; **7b**, 130798-22-0; **7c**, 130798-23-1; **8a**, 130798-24-2; **8b**, 130798-25-3; **8c**, 130798-26-4; **9a**, 130798-27-5; **9b**, 130798-28-6; **9c**, 130798-29-7; **10**, 130798-37-7; **11a**, 130798-38-8; **11b**, 130798-39-9; **11c**, 130798-40-2; GMP, 85-32-5.

Acidities of C2 Hydrogen Atoms in Thiazolium Cations and Reactivities of Their Conjugate Bases

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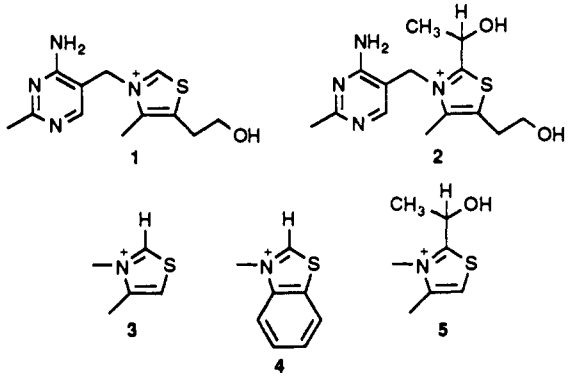
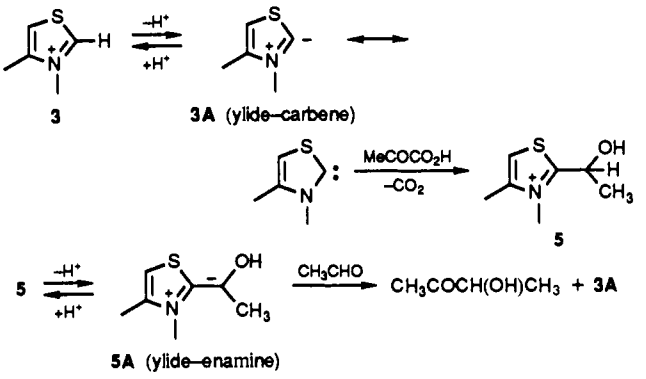
Abstract: The equilibrium acidity for the C2-H bond in the 3,4-dimethylthiazolium cation ($TZCH^+$), a model for thiamin, was estimated to be higher than 16 by direct titrations with indicators in DMSO solution. This result is in agreement with several earlier indirect estimates based on kinetic acidities and Brønsted plots, which place the acidity in the 16-20 pK_{HA^+} region in aqueous solution, but not with a direct titration in aqueous medium made under stopped-flow conditions, which placed the acidity in the region of $pK_{HA^+} \approx 13$. 3-Methylbenzothiazolium cation ($BZCH^+$), which was found to be considerably more acidic, reacted with Et_3N in DMSO to give a dimer BZC=CZB. Evidence is presented to show that this and similar dimerizations occur by addition of the conjugate base of $BZCH^+$ to the H-C=N^+ bond of the $BZCH^+$ thiazolium cation, followed by deprotonation. The conjugate base of $BZCH^+$ adds to $BZCH^+$ in preference to reacting with excess of electrophiles such as *t*-BuOH, PhCHO, or $PhCH{=}CH_2$. Amines, such as piperidine, add rapidly to less acidic thiazolium cations under conditions where little or no deprotonation occurs. These observations exclude a carbene mechanism for dimerization and amine adduct formation.

The conjugate bases obtained by removing the acidic C2 and C2α hydrogen atoms, respectively, from the thiazolium cation moieties of thiamin (**1**) and 2-(α-hydroxyethyl)thiamin (**2**) are effective in both enzymic and nonenzymic catalysis.[1,2] The acidities of **1** and **2** and those of related models, such as 3,4-dimethylthiazolium cation (**3**), 3-methylbenzothiazolium cation (**4**), and 2-(α-hydroxyethyl)-3,4-dimethylthiazolium cation (**5**), and the reactivities of their conjugate bases have therefore been a matter of considerable interest for the past three decades.[2]



Scheme I. Base-Catalyzed Reactions in Aqueous Buffers



The reactions by which the vitamin B_1 enzyme cofactors **1** and **2** exert their catalytic activity are illustrated with thiazolium ions **3** and **5** in Scheme I.

The first of these reactions is the catalytic decarboxylation of pyruvic acid, which is a primary function of thiamin pyrophosphate in nature. The product of this decarboxylation is **5**, which can either react with base to eliminate acetaldehyde and regenerate the ylide-carbene **3A** or be transformed in several steps to acetoin with the regeneration of **3A**. The ability of thiazolium cation models, such as **3**, to play the catalytic roles of **1** and **2** in the presence of basic aqueous buffers has been demonstrated in several investigations.[1,2] Futhermore, thiazolium cations, such as 3-

(1) Breslow, R. *J. Am. Chem. Soc.* **1958**, *80*, 3719-3726.
(2) For reviews, (see: (a) Gallo, A. A.; Mieyal, J. J.; Sable, H. Z. In *Bioorganic Chemistry*; van Tamelen, E. E., Ed.; Academic Press: New York, 1978; Vol. 4, pp 147-177. (b) Kluger, R. *Chem. Rev.* **1987**, *87*, 863-876.

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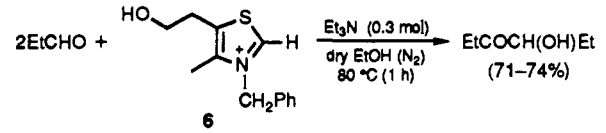
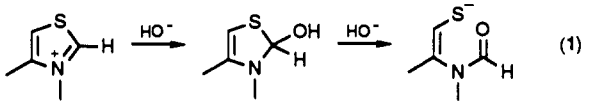
benzyl-4-methyl-5-(β-hydroxyethyl)thiazolium ion (**6**), have found synthetic applications in benzoin-type condensations in nonaqueous solvents, such as DMF or dry EtOH, as illustrated by the preparation of 4-hydroxy-3-hexanone.[3]



6

Equilibrium acidities of **1** and **3** cannot be measured in basic aqueous solution because the hydroxyl adduct of the thiazolium cation is formed rapidly and is subject to base-catalyzed ring opening (eq 1).[4]



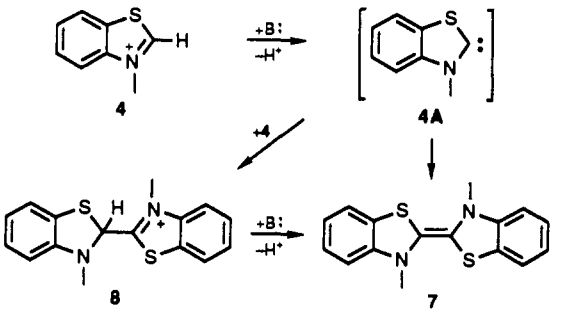
(1)

Estimates of thermodynamic acidities have therefore most often been made from kinetic acidity measurements. The pK_{HA^+} values for **1** and **3** estimated in this way generally range from 16 to 20.[2b,5] Much lower values ($pK_{HA^+} \approx 13$) were obtained by titrations carried out in aqueous borate buffer solutions under stopped-flow conditions,[6] but these values have been questioned on the grounds that the equilibria being measured were probably those between HO^- ion and the thiazolium cations, i.e., step 1 in eq 1, giving pK_{R^+} rather than pK_{HA^+} values.[7]

The conjugate base of **3** or similar thiazolium cations has never been isolated or observed spectroscopically, although its presence is suggested by Breslow's deuterium exchange studies,[1] and the suggestion has been made that its presence at physiological pHs in appreciable concentration is responsible for the catalytic activity of **3**. Thus, the corresponding oxazolium cations, despite their greater acidity, fail to act as catalysts, presumably because their faster rate of hydrolysis prevents a buildup of a sufficient concentration of ylide.[4a]

Breslow first recognized the possible importance of carbene character in the ylide.[1] Later work with tetrakis(dialkylamino)ethylenes, $(R_2N)_2C{=}C(NR_2)_2$, which were presumed to be dissociating readily to carbenes, $(R_2N)_2C{:}$, prior to reaction with electrophiles, led Wanzlick to propose in 1962 that the ylides derived from thiazolium salts of type **3** were reacting as "nucleophilic carbenes" with electrophiles.[8] However, later studies, in which mixtures of $(R_2N)_2C{=}C(NR_2)_2$ and $(R_2'N)_2C{=}C(NR_2')_2$ alkenes failed to give cross dimers on heating, ruled out the presence of free $(R_2N)_2C{:}$ carbene intermediates.[9] In the meantime, Quast and Huenig claimed to have succeeded in producing a short-lived nucleophilic carbene by deprotonating 3-methylbenzothiazolium ion (**4**) with Et_3N in CH_3CN and to have differentiated its reactions with azidium salts from those of the carbene dimer, which was also formed under these conditions.[10a] In the same year, Metzger and his associates

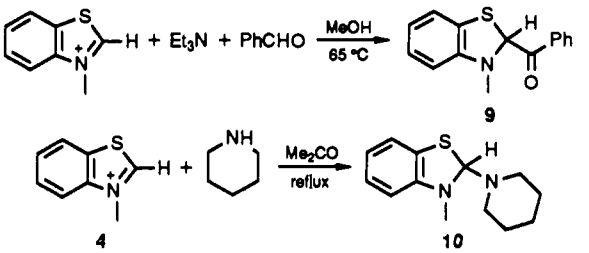
Scheme II.[a]



4 **4A** **8** **7**

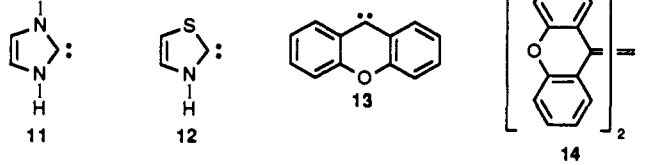
[a] **B:** = $Et_3N{:}$.

published a study of the formation of this presumed carbene dimer bi(3-methylbenzothiazolinylidene) (**7**) and its reactions with electrophiles.[11] Metzger suggested two mechanisms for the formation of **7** from **4** by the action of triethylamine in dry acetone (Scheme II). In the first mechanism, two molecules of an initially formed carbene **4A** react to form the dimer **7** directly. In the alternative mechanism, which he favored and which was also favored by Quast and Huenig,[10] it was assumed that the carbene was trapped by the precursor thiazolium cation **4** to give **8**. Deprotonation of **8** by the base then gave the dimer **7**. Metzger also found that adducts **9** and **10** were formed from reactions of **4** with benzaldehyde and Et_3N in dry MeOH and with excess piperidine in dry acetone. In 1984, Metzger repeated the suggestion that these and additional reactions of **4** involved carbene intermediates.[11b]



9 **4** **10**

Gleiter and Hoffmann pointed out in 1968 that the ground state of a carbene will generally be a triplet unless the difference in energy between the σ and p orbitals is greater than 2 eV. They suggested that one way to achieve this splitting is by interaction of the carbene electrons with an aromatic grouping of $(4n + 2)$ π electrons such as in **11**, which is calculated to have a σ–p splitting



11 **12** **13** **14**

of 3.45 eV. Large splittings were also predicted for carbenes isoelectric with **11**, such as **12**.[12] Lapin and Schuster have recently provided experimental support for these calculations by showing that xanthylidene (**13**) exhibits reactivities characteristic of a singlet carbene wherein the ground-state energy is at least 4 kcal/mol *lower* than that of the triplet carbene. One such reaction was direct coupling to form the dimer **14**, (bixanthylidene).[13]

The experiments of Lemal and of Winberg[9] apparently discouraged the interpretation of the behavior of the conjugate bases

(3) (a) Stetter, H. *Angew. Chem., Int. Ed. Engl.* **1976**, *15*, 639–712. (b) Stetter, H.; Kuhlmann, H. *Org. Synth.* **1983**, *52*, 170–175.

(4) (a) Duclos, J. M.; Haake, P. *Biochemistry* **1974**, *13*, 5358–5362. (b) El Hage Chahine, J.-M.; Dubois, J.-E. *J. Am. Chem. Soc.* **1983**, *105*, 2335–2340.

(5) (a) McNelis, E. Ph.D. Dissertation, Columbia University, New York, NY, 1960. (b) Crosby, J.; Lienhard, G. E. *J. Am. Chem. Soc.* **1970**, *92*, 5707–5716. (c) Kemp, D. S.; O'Brien, J. T. *J. Am. Chem. Soc.* **1970**, *92*, 2554–2555. (d) Washabaugh, M. W.; Jencks, W. P. *Biochemistry* **1988**, *27*, 5044–5053. (e) Zoltewwicz, J. A.; O'Halloran, J. K. *J. Org. Chem.* **1978**, *43*, 1713–1717.

(6) (a) Hopmann, R. F. W.; Brugnoni, G. P. *Nature (London), New Biol.* **1973**, *246*, 157–158. (b) Hopmann, R. F. W.; Brugnoni, G. P.; Fol, B. *J. Am. Chem. Soc.* **1982**, *104*, 1341–1344.

(7) Bunting, J. W. *Adv. Heterocycl. Chem.* **1979**, *25*, 1–82.

(8) Wanzlick, H. W. *Angew. Chem., Int. Ed. Engl.* **1962**, *1*, 75–77.

(9) (a) Lemal, D. M.; Lovald, R. A.; Kawano, K. I. *J. Am. Chem. Soc.* **1964**, *86*, 2518–2519. (b) Winberg, H. E.; Carnahan, J. E.; Coffman, D. D.; Brown, M. *J. Am. Chem. Soc.* **1965**, *87*, 2055–2056.

(10) (a) Quast, H.; Huenig, S. *Angew. Chem., Int. Ed. Engl.* **1964**, *3*, 800–801. (b) Quast, H.; Huenig, S. *Chem. Ber.* **1966**, *99*, 2017–2038.

(11) (a) Metzger, J.; Larive, H.; Dennilauler, R.; Barle, R.; Gaurat, C. *Bull. Soc. Chim. Fr.* **1964**, *11*, 2857–2867. (b) Metzger, J. In *Comprehensive Heterocyclic Chemistry*; Katritzky, A. R., Rees, C. W., Eds.; Pergamon Press: New York, 1984; pp 262–263.

(12) Gleiter, R.; Hoffmann, R. *J. Am. Chem. Soc.* **1968**, *90*, 5457–5460.

(13) Lapin, S. C.; Schuster, G. B. *J. Am. Chem. Soc.* **1985**, *107*, 4243–4245.

of thiazolium cations in terms of carbenoid-type species, and most subsequent investigators have viewed them as strongly basic ylides.[5] Recently, however, the dimerization of **4** and the addition of benzaldehyde to **4** under the basic conditions reported by Metzger[11] have been extended to 5-(ethoxycarbonyl)-3,4-dimethylthiazolium and related thiazolium cations.[14] The authors,[14] who were apparently unaware of the Lemal–Winberg results, revived the Wanzlick–Metzger carbene mechanism and have proposed, on the basis of circumstantial evidence, that dimerization occurs by direct carbene coupling. But, as has been pointed out by Washabaugh and Jencks,[15] these experiments do not rule out Metzger's indirect mechanism. In this paper, we describe direct acidity measurements in DMSO solution that show the pK_{HA^+} values for **3** and similar thiazolium cations are in the high region reported by several earlier investigators[5] rather than in the low region reported by Hopmann.[6] We also report experiments supporting the view[15] that the dimerization of conjugate bases derived from **3** and similar thiazolium ions in DMSO, or other nonhydroxylic solvents, occurs by Metzger's addition–elimination mechanism (Scheme II), but involves ylide rather than singlet carbene intermediates.

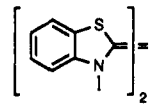
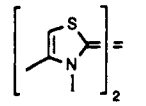
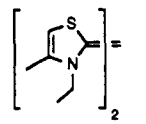
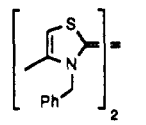
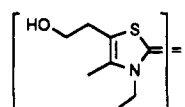
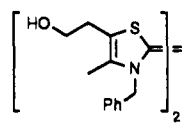
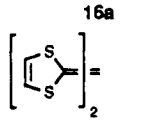
Results and Discussion

Acidities of Thiazolium Cations and Dimerization of Their Conjugate Bases. In a recent paper, we have shown that it is possible to measure acidities of 2-(α-methoxyethyl)-3,4-dimethylthiazolium cation (**5**, where the OH group has been protected by methylation) and similar 2-alkylthiazolium ions by carrying out direct three- (or more) point titrations with indicators in DMSO.[16] The pK_{HA^+} of methoxy **5** was found to be 14.1 ± 0.05, which was about 3 units lower than estimates based on kinetic acidities, but close to earlier preliminary measurements.[17] The early measurements had been carried out by one-point titrations, because the conjugate bases of 2-alkylthiazolium cations appeared to be unstable. Earlier titrations of **3** and **4** had also been carried out because it seemed likely that direct titrations with indicators would be successful, since the addition of hydroxide ion to the C=N$^+$ bond and subsequent ring opening (eq 1) that occurs in aqueous solution would be avoided. Experiment showed, however, that here too the indicator ion absorbance was not stable. One-point titrations[17] suggested that the pK_{HA^+} values were in the low region reported by Hopmann.[6]

In the recent studies of 2-alkylthiazolium ions, ^{1}H NMR and cyclic voltammetry (CV) were used to establish the existence of an acid–base equilibrium.[16] This was not possible in the present instance. Treatment of a DMSO solution of an indicator ion (9-phenylfluorenide ion, pK_{HA} = 17.9) with a DMSO solution of 3,4-dimethylthiazolium cation (**3**) caused the color to fade immediately, suggesting either that **3** was much more acidic than the indicator or that the conjugate base of **3** was unstable. Similar results were obtained with indicator bases having pK_{HA} values above pK_{HA} = 12. No reaction occurred with weaker bases.

Cyclic voltammetric measurements revealed that, when 1 equiv of **3** in DMSO was added to a DMSO solution of 9-phenylfluorenide ion, the irreversible CV peak characteristic of 9-PhFl$^-$ ion at −0.137 V was replaced by a *reversible* CV peak at −0.066 V, consistent with a proton transfer followed by further reaction of the conjugate base. The reversible peak at −0.066 V was reminiscent of one that we had observed previously for tetrathiafulvene (TTF) and suggested that the product formed might be similar to Metzger's dimer **7**. An authentic sample of **7** was prepared by reaction of **4** with Et_3N in acetone by the method of Metzger.[11] Its ^{1}H NMR and mass spectrum were consistent with the structure assigned to **7**, and its CV in DMSO was identical with that obtained on treatment of **4** in DMSO with anionic bases such as carbazolide anion (pK_{HA} = 19.9) or 9-*t*-BuFl$^-$ ion (pK_{HA} = 24.35). The difference that we observed between the redox potential of **7** and that for TTF of 0.54 V also proved to be nearly the same as one previously reported (0.47–0.50 V).[18,19] Data on the cyclic voltammograms obtained by treatment of **3**, **4**, and similar thiazolium salts with CH_3SOCH_2K or other bases along with the structures of the dimers formed are shown in Table I.

Table I. Redox Potentials for the Dimers Formed from Reactions of Thiazolium Salts with Bases at Ambient Temperature

dimer	E_1[a]	E_2[b]	$E_1 - E_2$
 **7**	0.305 0.323[c]	0.250 0.259[c] 0.177[d]	0.055 0.065
 **15**	−0.062 −0.028[c]	−0.128 −0.085[c]	0.066 0.056
 **15a**	−0.020	−0.067	0.047
 **15b**	0.041 0.017[c]	−0.015 −0.046[c]	0.056 0.063[c]
 **16**	−0.076 0.095[c]	−0.019 −0.002[c]	0.035 0.097[c]
 **16a**	0.019	−0.036	0.055
 **17 (TTF)**	0.840[c]	0.775[c] 0.700[c] 0.670[d]	0.065

[a] Potential for the oxidation peak obtained by cyclic voltammetry with a Ag/AgI electrode in DMSO, unless otherwise noted. The Ag/AgI electride is −0.370 V vs SCE. [b] Potential of the reduction peak. [c] In CH_3CN; the dimers were more stable in this solvent. The CVs of 3-methylbenzothiazolium and 3,4-dimethylthiazolium salts when treated with base in CH_3CN consisted of two successive reversible oxidations. [d] Values from ref 18 referred to Ag/AgI by addition of 0.370 V.

Examination of Table I shows that changing the N substituent from methyl to ethyl to benzyl causes E_1 in **15** to shift to progressively more positive potentials. These shifts, and the much larger shift for the benzo fusion in **7**, are associated with decreases in the electron density on nitrogen caused by polarization and/or delocalization of the lone pair on nitrogen. The change in E_1 from **15** to **7** is 0.367 V (8.5 kcal/mol).[19] Replacement of the *N*-CH_3

(14) Doughty, M. B.; Risinger, G. E. *Bioorg. Chem.* **1987**, *15*, 1–14.
(15) Washabaugh, M. W.; Jencks, W. P. *J. Am. Chem. Soc.* **1989**, *111*, 674–683.
(16) Bordwell, F. G.; Satish, A. V.; Jordan, F.; Rios, C. B.; Chung, A. C. *J. Am. Chem. Soc.* **1990**, *112*, 792–797.
(17) Singer, D. L. Ph.D. Dissertation, Northwestern University, Evanston, IL, 1981.
(18) (a) Wheland, R. C.; Gillson, J. L. *J. Am. Chem. Soc.* **1976**, *98*, 3916–3925. (b) Coffen, D. L.; Chambers, J. Q.; Williams, D. R.; Garrett, D. E.; Canfield, N. D. *J. Am. Chem. Soc.* **1971**, *93*, 2258–2268.
(19) It seems likely that **7** and similar dimers reported here have trans structures, but this remains to be established.

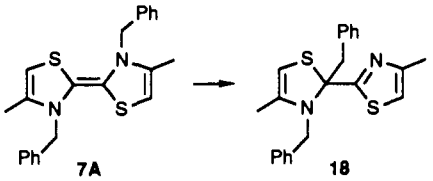
Table II. Estimates of the Acidity of **3** in DMSO by Extrapolations of Indicator Absorbances

run	$[In^-]_0$[a]	$[HIn]_0$[a]	$[HA^+]_0$[a]	abs (t)[b]	$[A^+]$[c]	pK_{HA^+}[d]
1	0.80	0.93	0.972	0.448 (12)	0.005	16.3
2	0.78	0.91	1.84	0.420 (5)	0.040	15.7
3	0.80	0.86	1.67	0.430 (4)	0.040	15.6
4	0.71	1.07	0.768	0.380 (7)	0.001	16.6
5	0.68	1.066	1.78	0.368 (14)	0.003	16.7
6	0.627	1.08	2.60	0.310 (5)	0.060	15.5
7	1.22	2.25	1.95	0.645 (8)	0.070	15.2
8	1.02	2.79	2.45	0.575 (9)	0.050	15.4

[a] Concentration (mM) at t_0. [b] Absorbance extrapolated from a plot of Abs vs t. The estimated time lag (s) prior to the start of the absorbance reading is given in parentheses. [c] Concentration of ylide (mM) corresponding to the extrapolated absorbance and pK_{HA^+}. [d] Calculated from our pK_{HA} program.

moiety in **15** by S (to give TTF) causes a shift of 0.906 V (20 kcal/mol).

The CV spectra for the *N*-CH_2Ph derivatives faded with time, and a stable irreversible peak appeared. This instability is not unexpected since dimers of this type are known to undergo sigmatropic 1,3-shifts readily on heating to give a more stable, rearranged dimer **18**.[20]



Preliminary stopped-flow rate studies showed that the $t_{1/2}$ for dimer formation was in the millisecond time scale. The rapid and complete fading of the indicator ion absorbance for reactions of **3** with indicators in the 13–18 pK_{HA} range does not provide information concerning the acidity since both the rate of proton transfer and the rate of dimerization are fast reactions. Addition of an aliquot of **3** to a DMSO solution of 9-PhSFl$^-$ ion (pK_{HA} = 15.4) caused a very rapid drop in In^- ion absorbance. Attempts to extrapolate the absorbance back to t_0 were unreliable, however, because the reaction was so fast that only the tail end of the absorbance drop could be recorded. Experiments with a less basic indicator HZFP2 (the 4-chlorophenylhydrazone of fluorenone, pK_{HA} = 14.15) were more successful. By starting the recorder and adding the solution of **3** to mixtures of In^- and HIn in DMSO simultaneously, we found that an early portion of the absorbance vs time curve could be observed. If we assume that the rate of establishment of the acid–base equilibrium (eq 2) is faster than

$$In^- + HA^+ \rightleftharpoons InH + A^{\pm} \qquad (2)$$

the rate of dimerization, as seems likely, extrapolation of the absorbance back to t_0 will give at least a rough estimate of the pK_{HA^+} of the thiazolium ion. The results of calculations of pK_{HA^+} made from eight runs wherein the concentrations of In^-, HIn, and HA^+ were varied are shown in Table II.

Examination of Table II shows that the estimated pK_{HA^+} values for 3,4-dimethylthiazolium cation (**3**) varies between 15.4 and 16.7. The lower values are associated with higher ylide $A^{\pm}$ concentrations. Increases in $[A^{\pm}]$ lead to a faster rate of dimerization (k_2) and perturb the equilibrium in eq. 3. Hence, the entries

$$HA^+ + In^- \underset{k_{-1}}{\overset{k_1}{\rightleftharpoons}} InH + A^{\pm} \xrightarrow{k_2} A\text{–}A \qquad (3)$$

where the concentration of $A^{\pm}$ is of the order of 0.003 mM are more accurate. The average of the three entries with low concentrations of $A^{\pm}$ is 16.5. These titrations therefore show that the pK_{HA^+} for **3** in DMSO is about 16.5 or higher. These results are in agreement with the values in the pK_{HA^+} range of 16–20 in H_2O arrived at by earlier workers from rates of deuterium exchange and Brønsted correlations[5,15] but are contrary to the direct measurements of a presumed acid–base equilibrium in water.[6] The measurements in DMSO are pertinent to those in water since it has been shown that, for several different thiazolium and alkylammonium ions, the pK_{HA^+} values in DMSO and H_2O are within ±1 pK_{HA^+} unit of one another.[16,21]

Attempts To Trap the Conjugate Base of 4. 3-Methylbenzothiazolium ion (**4**) forms dimer **7** rapidly in DMSO on treatment with Et_3N (pK_{HA^+} for Et_3NH^+ is 9.0[21]), but 3,4-dimethylthiazolium ion (**3**) is too weak an acid to form the dimer under these conditions (the pK_{HA^+} value of **4** may be as low as 12 by analogy with the 5.4 pK_{HA^+} difference in values between 2,3-dimethylbenzothiazolium and 2,3,4-trimethylthiazolium cations[16]). Addition of Et_3N to a DMSO solution containing equivalent amounts of **4** and an electrophile-trapping agent should therefore generate small quantities of the carbene–ylide conjugate base of **4** in the presence of a larger excess of electrophile. Experiments with the following electrophiles failed to inhibit dimer formation: (a) *t*-BuOH, (b) H_2O, (c) PhOH, (d) $Me_2C{=}O$, (e) PhCHO, or (f) $PhCH{=}CH_2$. The xanthylidene carbene **13** is a possible model for Metzger's carbene **4A**. Carbene **13** is rather selective in its reactions. It fails to react with saturated hydrocarbons by insertion or hydrogen-atom abstraction. It fails to add to the C=C bonds or ordinary alkenes but does add to styrenes.[13] It is highly reactive towards *t*-BuOH, however, forming 9-*tert*-butoxyxanthene with $k = 3.4 \times 10^9$ M^{-1} s^{-1} in pentane.[13] The failure of **4A** to react with *tert*-butyl alcohol, styrene, or the other electrophiles shows that the conjugate base of **4** does not display carbenoid character. Instead, it behaves as an ylide and adds rapidly to **4**. Dimer formation is completed by deprotonation. In other words, dimerization occurs by Metzger's addition–elimination mechanism (Scheme II), but the conjugate base is not behaving as a carbene. Since the ylide derived from **3** reacts at a diffusion-controlled rate with H_3O^+,[15] the failure of PhOH, H_2O, or *t*-BuOH to inhibit dimerization of **4** may, at first sight, seem surprising. It must be remembered, however, that these hydroxylic acids are relatively weak in DMSO (pK_{HA}'s of 18, 32, and 32, respectively[22]) and that the acid–base reactions are reversible. Dimerization of **4** in DMSO is inhibited completely by the presence of 1 equiv of piperidine or pyrrolidine. The adducts formed by reactions of these bases with **4** in CH_3CN (e.g., **10**) have been isolated and identified. Since small concentrations of the conjugate base of **4** are no doubt formed in these reactions, it was conceivable, although unlikely, that the adducts could be formed by a carbene mechanism.[23] Similar adduct formation was observed, however, by reaction of pyrrolidine or morpholine with **3** and similar thiazolium cations in DMSO. Since the pK_{HA^+} values for these amines in DMSO are about 5–7 units below that of **3** or similar thiazolium ions, this observation rules out deprotonation ("carbene formation") as a first step in adduct formation. Instead, the amine must add directly to the thiazolium cation. Deprotonation then gives the adduct.

Formation of Cross-Coupled Dimers. It was of interest to see whether it would be possible to form cross-coupled dimers by reaction of the conjugate base of **4** with other thiazolium cations such as **3**. Addition of Et_3N to a DMSO solution containing equivalent concentrations of **3** and **4** gave only dimer **7**, indicating that the conjugate base of **4** adds selectively to **4** in the presence of **3**. When, however, aliquots of CH_3SOCH_2K were added to a mixture of equivalent amounts of **4** and 3-ethyl-4-methylthiazolium ion (**3'**), **7** was the initial product, but a cross-coupled product was formed as a secondary product and finally the dimer derived from **3'** appeared (Scheme III and Figure 1).

Spectrum a in Figure 1 is essentially that of dimer **7**, but a small shoulder for the cross-dimer **19** is present. Since **4** is much more

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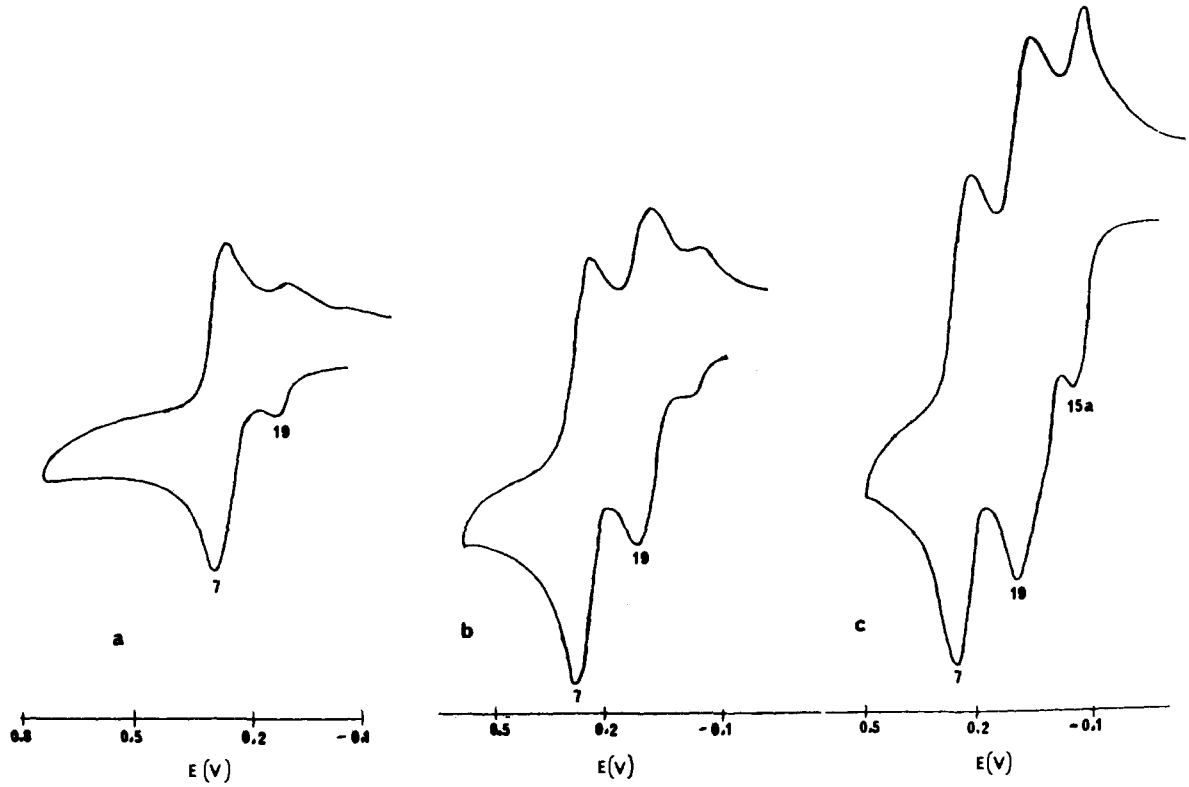
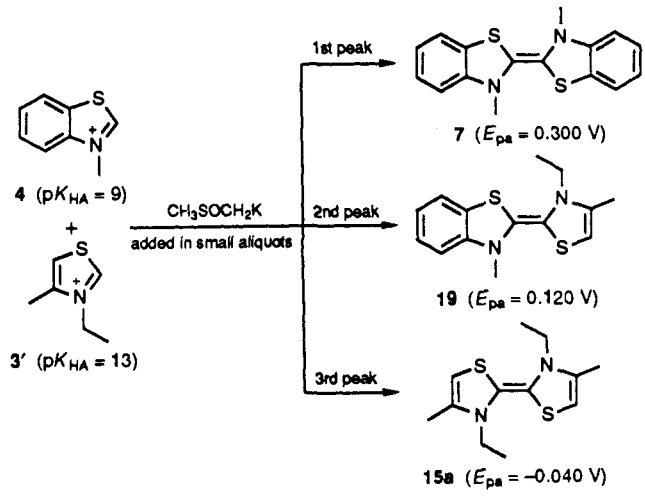


Figure 1. Cyclic voltammograms. Spectrum a shows the reversible oxidation peak at 0.300 V, characteristic of dimer **7**, formed by addition of about 0.3 equiv of CH_3SOCH_2K in DMSO to an equimolar mixture of 3-methylbenzothiazolium methyl sulfate and 3,4-dimethylthiazolium iodide in DMSO. Spectrum b shows the result of addition of another aliquot of base. The small shoulder at 0.120 V due to cross-dimer **19** in spectrum a has now grown into a second peak. Spectrum c shows the results of addition of a third aliquot of base. Peaks for all three dimers, **7**, **19**, and **15a** are now apparent.

Scheme III



acidic than **3**, one would expect its conjugate base to be present in larger amount. Evidently, the conjugate base of **4** reacts selectively with **4**, in preference to **3**, and deprotonation gives **7**. Addition of a second aliquot of base generates relatively more of the conjugate base of **3** since the concentration of **4** has been depleted, and more **19** is formed. By the time the third aliquot of base is added, **3** is in sizable excess and more **19** plus the dimer of **3** (**15a**) are the principal products.

Experimental Section

NMR spectra were recorded on a Varian EM-390 or XLA-400 spectrometer. Mass spectra were measured by Dr. H. L. Hung on an HP 5985 GC/MS instrument. Melting points were determined on a Thomas Hoover capillary melting point apparatus and are uncorrected. A sample of 3-benzyl-4-methylthiazolium chloride was generously provided by Prof. W. P. Jencks and M. Washabaugh, Brandeis University, Waltham, MA. The indicators and trapping reagents used are commercially available or have been reported earlier. The procedure for electrochemical measurement has been described earlier,[16] and all potentials reported are referenced to Ag/AgI electrode.

3-Methylbenzothiazolium Methyl Sulfate. To a solution of benzothiazole (8.1 mL) in benzene (15 mL) under nitrogen was added dropwise a solution of dimethyl sulfate (7.1 mL) in benzene (15 mL). When the mixture was heated to reflux temperature, crystals started to precipitate. Heating was continued for an additional 10 min, and the solution was cooled. The crystals were separated by filtration, washed with ether, and dried under reduced pressure; mp 125–128 °C.

3,4-Dimethylthiazolium Iodide (3-I). To 4-methylthiazole (2 mL) dissolved in absolute ethanol (20 mL) was added methyl iodide (4 mL). The mixture was stirred at 40 °C for 2 days. On cooling, the salt crystallized. The mixture was diluted with ether, and the crystals were separated by filtration and washed with ether. The crude salt was crystallized from a hot ethanol–ether mixture, and the crystals were dried under reduced pressure: 4.3 g, 95% yield; mp 117–118.5 °C (lit.[5c] mp 118–119 °C).

3-Ethyl-4-methylthiazolium Bromide (3'-Br). To a solution of 4-methylthiazole (2 mL) in dry acetonitrile (5 mL) was added bromoethane (2 mL), and the solution was heated at reflux temperature for 24 h. The solvent was removed under reduced pressure and the residue recrystallized from a hot ethanol–ether mixture. Drying under reduced pressure gave white crystals: 2.1 g, 55% yield; mp 169–171 °C (lit.[1] mp 170–171 °C).

3-Ethyl-5-(α-hydroxyethyl)-4-methylthiazolium bromide was prepared following the procedure described by Stetter:[3] mp 84–85 °C (lit.[3] mp 85–86.5 °C). **3-Benzyl-5-(α-hydroxyethyl)-4-methylthiazolium chloride** was prepared according to the procedure described by Stetter;[3] mp 139–140.5 °C (lit.[3] mp 140–140.5 °C).

Bi(3-methylbenzothiazolinylidene) (7). This dimer was prepared according to the procedure described by Metzger:[11] mp 162 °C (lit.[11] mp 162 °C); MS, *m/e* (relative intensity) 299 (9), 298 (39), 283 (100), 149 (20), 148 (28). The parent peak is *m/e* 298; *m/e* 283 corresponds to loss of CH_3, and *m/e* 149 is the carbene **4A**. The bright yellow crystalline dimer tarnished when exposed to air but was stable under argon or in solution. A solution of the dimer in DMSO undergoes reversible oxidation by cyclic voltammetry (E_{pa} = 0.310 V; $E_{pa} - E_{pc}$ = 0.055 V). The oxidation potential is within experimental error of that of the product formed in DMSO from 3-methylbenzothiazolium methyl sulfate in the presence of Et_3N. When sodium bis(trimethylsilyl)amide was used as the base, the CV showed an irreversible oxidation. A similar change to

irreversible oxidation was observed when $((CH_3)_3Si)_2NH$ was added to the solution of dimers showing a reversible oxidation, thus suggesting that the radical cation of the dimer is unstable in the presence of $((CH_3)_3Si)_2NH$, the conjugate acid of sodium bis(trimethylsilyl)amide.

In an attempt to isolate the dimer of 3-ethyl-4-methylthiazolium bromide (bi(3-ethyl-4-methylthiazolinylidene) (**15a**)), a dilute solution of 3-ethyl-4-methylthiazolium bromide (**3'**-Br) (25 mg in 10 mL) in acetonitrile under argon was treated with sodium bis(trimethylsilyl)-amide. The supernatant solution obtained on centrifugation was transferred to another flask flushed with argon, and the solvent was removed by a current of argon. Needlelike crystals were obtained: MS, *m/e* (relative intensity) 287 (8), 286 (34), 144 (23), 143 (100). The peak with *m/e* 286 represents $M^+ + 32$, which is probably the adduct of the dimer (MW = 254) with oxygen, and the peak with *m/e* 143 represents 3-ethyl-4-methyl-Δ^4-thiazolin-2-one formed by fragmentation of the adduct. This dimer (**15a**) is more sensitive to oxygen than the benzo-fused dimer **7**.

3-Methyl-2-piperidinylbenzothiazolidine (10). Argon was bubbled through a solution of 3-methylbenzothiazolium methyl sulfate (0.5 g) in CH_3CN (10 mL). To this solution was added in one portion the secondary amine piperidine or pyrrolidine (0.5 mL, 3 equiv). After the clear solution was stirred for an additional 5 min, the solvent and excess amine were removed under reduced pressure. The residue was dissolved in ether and washed with water, and the organic layer was dried over anhydrous sodium sulfate. Solvent removal gave an oily layer, which solidified on cooling in the refrigerator. Piperidine adduct: mp 78–81 °C (crystallized from hexane) (lit.[11] mp ≈ 88 °C); ^{1}H NMR ($CDCl_3$) δ 7.25–6.12 (m, 5 H), 2.93 (s, 3 H), 2.48–2.19 (m, 4 H), 1.77–1.28 (m, 6 H); MS, *m/e* (relative intensity) 234 (6), 151 (12), 150 (100), 84 (23). Pyrrolidine adduct: mp 30 °C; ^{1}H NMR ($CDCl_3$) δ 7.12–6.20 (m, 5 H), 2.93 (s, 3 H), 2.78–2.26 (m, 4 H), 1.88–1.50 (m, 4 H); MS, *m/e* (relative intensity) 220 (2.4), 165 (4.5), 151 (4), 150 (40), 70 (49), 69 (10), 43 (100).

The formation of adducts from the reactions of excess secondary amines with thiazolium cations was followed electrochemically. **3-I**, 3-ethyl-4-methylthiazolium bromide, and thiamin chloride all had irreversible reduction peaks between −0.900 and −0.997 V, which gave way within a few minutes to new irreversible peaks in the region of −0.662 to −0.688 on addition of 6-equiv aliquots of piperidine or pyrrolidine. Additional base was required to elicit a similar response from the weaker base morpholine. The pK_{HA^+} values of morpholinium perchlorate and pyrrolidinium chloride in DMSO were determined by titration to be 8.8 and 11.2, respectively.

Trapping Experiments. (a) In initial trapping experiments, the conjugate base of **4** was generated with indicator bases in the presence of potential trapping agents. An indicator (9-phenylfluorene or carbazole (5 mg)) and tetraethylammonium tetrafluoroborate (108 mg) were weighed into an electrochemical cell and dissolved in DMSO (5 mL). The CV of the solution was recorded after 0.3–0.4 equiv of CH_3SOCH_2K was added in aliquots. The (trapping) reagent (35–40 mg, 4–6 equiv) was added and the CV recorded to be sure that the reagent did not affect the CV of the indicator anion. To this solution were added 7–10 mg of 3-methylbenzothiazolium methyl sulfate or 3,4-dimethylthiazolium iodide. The solution was stirred and the CV recorded. In the absence of any trapping reagent, the peak height for the oxidation of the dimer was half of that of the oxidation of the indicator anion just before addition of the salt. These experiments showed that trapping reagents t-C_4H_9OH and CH_3COCH_3 do not affect the amount of dimer formed even when present in excess of 4 equiv. Diminution of the peak height was observed, however, with water.

(b) These preliminary results were verified and extended with Et_3N as base and the peak height of **7** relative to a standard where no electrophile has been added. The trapping reagent (7–10 mg) was weighed into an electrochemical cell. One equivalent of 3-methylbenzothiazolium methyl sulfate, tetraethylammonium tetrafluoroborate (108 mg), and DMSO (5 mL) were added to the cell. Triethylamine in acetonitrile (3 equiv) was added in aliquots and the CV recorded after each addition. Preliminary qualitative experiments showed that the trapping reagents PhOH, t-C_4H_9OH, CH_3COCH_3, Ph_3P, styrene, and (*E*)-CNCH=CHCN do not affect the amount of dimer formed even when present in excess of 3 equiv. For comparison, a blank experiment without a trapping reagent was run. The CV potentials and peak heights were as follows: standard, 0.310 ± 0.030 V, 5.5 mm; PhCHO, 0.298 V, 5.2 mm; t-BuOH, 0.298 V, 4.9 mm; H_2O, 0.298 V, 5.8 mm; PhOH, 0.319 V, 5.4 mm; $PhNH_2$, 0.327 V, 5.3 mm. No further diminutions in peak heights for PhOH, t-BuOH, Me_2C=O, or CNCH=CHCN were observed when large excesses (up to 50 equiv) were used.

Cross-Coupling Experiments. 3-Methylbenzothiazolium methyl sulfate (2.7 mg), 3,4-dimethylthiazolium iodide (2.7 mg), and tetraethylammonium tetrafluoroborate (108 mg) were weighed into an electrochemical cell. DMSO (5 mL) was added and argon bubbled through the solution. The CV of the solution obtained after addition of the first aliquot (0.05 mL, 150 mM) of CH_3SOCH_2K solution showed strong reversible oxidation at 0.289 V (Figure 1, curve a). Addition of another aliquot of base showed two reversible oxidation peaks at 0.315 and 0.135 V (Figure 1, curve b). Addition of yet another aliquot of base solution gave a CV with three reversible oxidations 0.289, 0.135, and −0.028 V (Figure 1, curve c). 9-Fluorenone (2,4-dichlorophenyl)hydrazone (5 mg; pK_{InH} = 12) and tetraethylammonium tetrafluoroborate (108 mg) were weighed into the electrochemical cell. To this mixture was added DMSO (5 mL), and argon was bubbled through it. A solution of CH_3SOCH_2K in DMSO (0.5 equiv) was added in aliquots. The CV recorded after each addition showed irreversible oxidation at 0.434 V. A mixture of 3-methylbenzothiazolium methyl sulfate (4 mg) and 3,4-dimethylthiazolium iodide (4 mg) dissolved in DMSO (0.1 mL) was added. The CV showed only one strong reversible oxidation at 0.300 V.

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