are measured to be. If we take into account these tendencies, then the semiempirical methods do quite well in predicting the relative order of acidities in these compounds. For example, in 1-methylpyrrole they correctly predict that the methyl hydrogens are the most acidic followed by the 2- and then the 3-hydrogens. The ordering of the 2- and 3-hydrogens in furan and thiophene is also predicted correctly, as is the relative acidity of the methyl group in 2-methylfuran. Among the methylpyridines, the 4-methyl is correctly predicted to be the most acidic with the 2- and 3-methylpyridines being nearly the same acidity both by calculation and by experiment. The only major error in the calculations occurs in pyridine itself, where the 2-position is predicted to be much more acidic than either the 3- or 4-position while it is found experimentally to be the least acidic of the three. This calculational error undoubtedly arises from the underestimation of the repulsion between the lone pair on the carbanion and the adjacent lone pair on nitrogen, which are constrained by the geometry of the anion to be in the same plane. An analogous situation occurs in the neutral analogues of these anions, namely the diazabenzenes, in which the nitrogen lone pairs are in the plane of the ring. In pyridazine the two nitrogens are adjacent so that lone-pair repulsion is expected to be large, and this isomer is calculated to be more stable (i.e., to have a lower heat of formation) than is found experimentally by 11 kcal/mol in the case of AM1 and 23 kcal/mol in the case of MNDO.[23] For pyrimidine and pyrazine, where the two nitrogens are farther apart, the discrepancies between theory and experiment are much smaller (3 and 10 kcal/mol for AM1 and MNDO, respectively). In the anion derived from 1-methylpyrrole by abstraction of the 2-hydrogen, the lone pair on the carbon and the lone pair on the adjacent nitrogen are orthogonal, and so interaction is minimized. In this case the calculated and experimental acidities agree quite well, despite the fact that both AM1 and MNDO do poorly in calculating the heat of formation of pyrrole itself. Obviously this error, whatever its source, occurs in both the neutral and the anion and so cancels in the calculation of the acidity.

Taft has noted a similar effect of adjacent lone pairs on the relative basicity of pyridazine and pyrimidine and on the relative gas-phase acidity of pyrazole and imidazole.[24] Catalan and co-workers have carried out both semiempirical and ab initio calculations on these and other heterocycles, including pyridine.[25] They find that among the semiempirical methods, only INDO handles this effect correctly; by this method they predicted the 4- and the 3,5-positions in pyridine to be the most acidic with the 2,6-positions much less acidic, in agreement with our data.

We plan to extend these investigations to other heteroaromatic systems, both to gain experimental insights into the ways carbanions are stabilized and to make further comparisons between experiment and theory.

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# Postulation of Bis(thiazolin-2-ylidene)s as the Catalytic Species in the Benzoin Condensation Catalyzed by a Thiazolium Salt plus Base

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Thiazolin-2-ylidenes generated by desilylation of 2-(trimethylsilyl)thiazolium ions are used as catalysts for the benzoin condensation. The experimental results together with theoretical calculations lead to the postulate that bis(thiazolin-2-ylidene)s, and not thiazolin-2-ylidenes, are the catalytic species in the benzoin condensation catalyzed by thiazolium salts plus base.

The benzoin condensation can be catalyzed by cyanide ion,[1-3] thiazolium salts **1** plus bases,[4,5] or bis(thiazolin-2-ylidene)s **2**.[6,7] Bis(thiazolin-2-ylidene)s can be formed by deprotonation of thiazolium ions with concomitant nucleophilic attack of the resulting thiazolin-2-ylidenes (or conjugate bases of thiazolium ions) **3** on the thiazolium ions.[8-11] Reaction of **2** with an electrophile gives the same derivative as that from reaction of **1** and the electrophile; the mechanism for this behavior was proposed by Lemal.[12]

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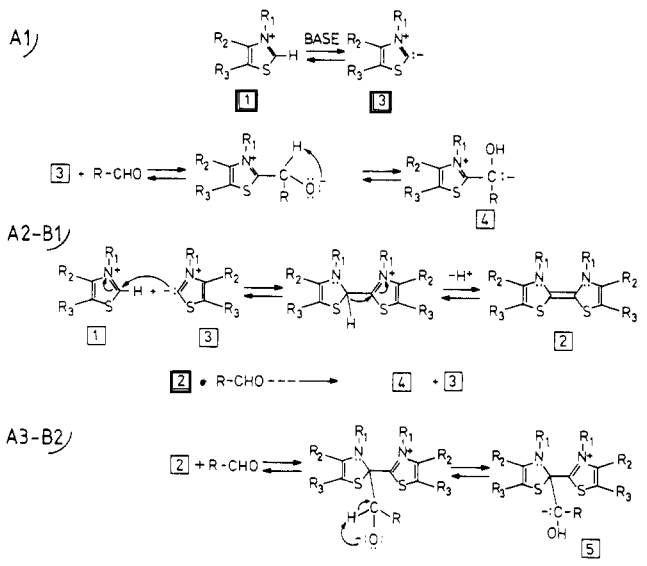
0022-3263/88/1953-4433$01.50/0 

**Scheme I**




Bis(thiazolin-2-ylidene)s are often referred to as dimers of thiazolin-2-ylidenes.

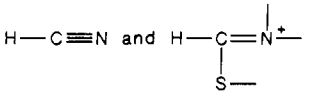
Several possible mechanisms must be considered in attempting to relate the catalytic activity of **1** plus bases to that of **2**.

**(A) Compound 1 plus bases (Scheme I)**: (A1) The actual catalytic species are **3** and the active aldehyde intermediates are Breslow intermediates **4**; (A2) formation of **2** takes place and a Lemal mechanism affords **4**; (A3) **2** are formed from **1** and then react with aldehydes to give reactive intermediates **5**.

**(B) Mechanisms related to the use of preformed 2 (Scheme I)**: (B1) Breslow intermediates **4** are formed as in mechanism A2; (B2) reactive intermediates **5** are formed as in mechanism A3.

## Analysis of Existing Data

More than 25 years ago, the formal electronic analogy between



and the relatively facile hydrogen isotope exchange at $C_2$-H of the thiazolium ring led Breslow to propose the mechanism represented in Scheme IIa.[13] The proposal was supported by showing[14] that 3-benzyl-4-methyl-2-(1-hydroxyethyl)thiazolium ion catalyzes the acetoin condensation in a protic solvent.

Breslow's proposal has achieved the status of a well-established mechanism and has led authors in the field[6,7] to the assumption that bis(thiazolin-2-ylidene)s also give rise to Breslow intermediates **4** (Scheme I). However, there are some observations that raise questions about this mechanism.

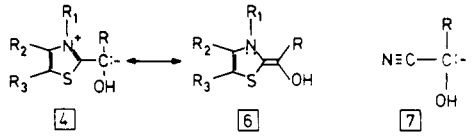
(1) Use of 3-benzyl-4-methyl-2-(1-hydroxyethyl)thiazolium ion in experiments with aldehydes other than acetaldehyde[15] affords mixtures of four acyloins, showing that the compound decomposes under the reaction conditions into acetaldehyde and 3-benzyl-4-methylthiazolium cation, and that a benzoin condensation then takes place among the mixture of the two aldehydes.

(2) With cyanide catalyst, the benzoin condensation is limited to aldehydes with no hydrogen on the $\alpha$ carbon (typically aromatic aldehydes), whereas a thiazolium salt plus a base extends the reaction to aliphatic aldehydes.[16] It should be remembered that thiamine is a biologically important thiazolium salt.[17]

Although thiazolin-2-ylidenes must be stronger bases than cyanide ion because thiazolium ions ($pK_a$ = 18) are weaker acids than HCN, they do not induce aldol reactions. A possible explanation is that they are removed from the medium as fast as they are formed by conversion into **2**; Hünig[19] and Balli[20,21] have established that the intermediates in the benzoin condensation with 3-alkylbenzothiazolin-2-ylidene catalyst are not isolable and are extremely short-lived. However, if this explanation were correct, the Lemal mechanism (in which free thiazolin-2-ylidenes are formed together with Breslow intermediates) would be excluded.

(3) As reported by Wanzlick and co-workers[6] and by ourselves,[22] **2** are better catalysts than the related **1** plus a base. The simplest explanation of this fact is that intermediates **5** play a decisive role in the mechanistic sequence (Scheme IIb), and that the concentration of **5** is higher when preformed **2** is used.

(4) Our MNDO calculations (see below) confirm that Breslow intermediates are, essentially, normal neutral species **6**, in spite of being customarily written in their zwitterionic form **4**. On the other hand, intermediates **5** are true carbanions, as the Lapworth intermediates **7** in cyanide catalysis.



Breslow intermediates, which are enols, should easily tautomerize to acylthiazolines. In fact, low yields in the benzoin condensation are accompanied by formation of 2-acylthiazolines. Metzger and co-workers[9] have shown that benzaldehyde affords 3-methyl-2-benzoylbenzothiazoline in 70% yield in the presence of 3-methylbenzothiazolium salt plus triethylamine. The observation of Wanzlick and co-workers[6] that some acylthiazolines cannot be used as active aldehyde equivalents in benzoin condensations is hard to fit into hypothesis A1.

(5) Under conventional conditions (**1** plus triethylamine), **3** are generated in very low concentrations because thiazolium ions are very weak acids; consequently, if they were the catalytic species, neat generation of them in higher concentration by decarboxylation of the corresponding betaines[23,24] should be an excellent way to perform benzoin condensations with minimal quantities of precatalyst. However, although 4,5-dimethylthiazolium-2-carboxylate (**8**) is an efficient and clean alternative precatalyst, it must

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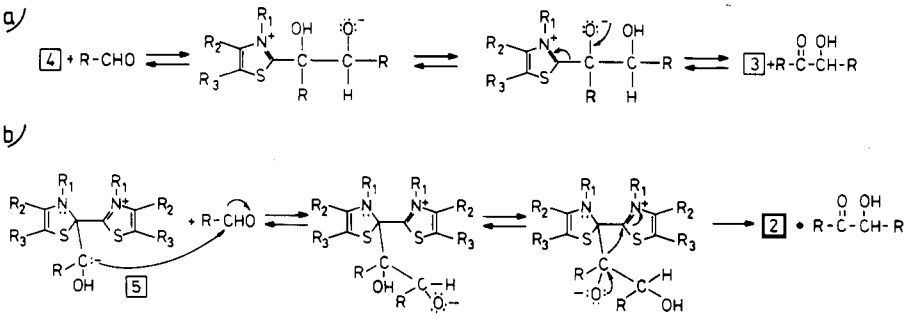
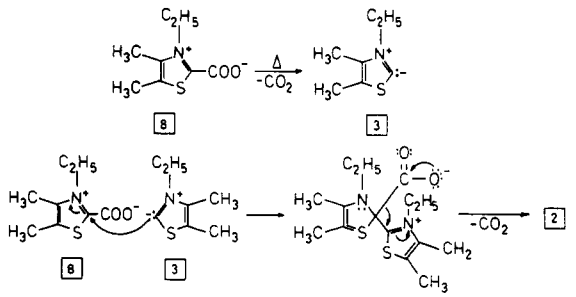
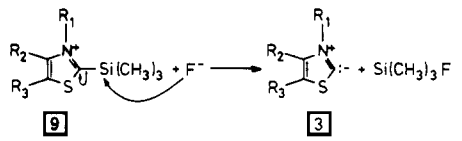
**Scheme II**



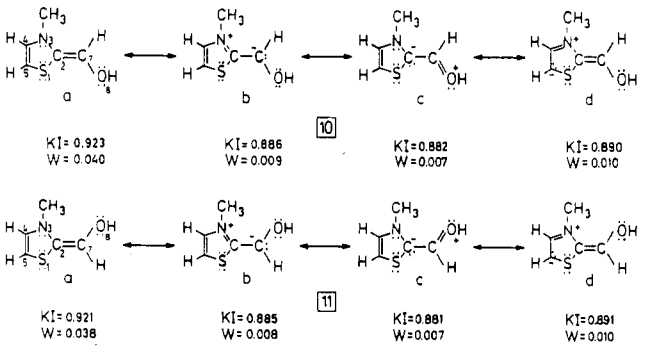
**Scheme III**



**Scheme IV**



**Scheme V**



be used in the same amount as those used in the conventional system to afford similar yields.[25] This result can be rationalized by invoking **2** as the actual catalytic species: a thiazolium-2-carboxilate should be an even better electrophile than a thiazolium ion, and formation of 2 should occur according to Scheme III. Use of a low precatalyst concentration would disfavor the formation of **2**.

## Experimental Results

We report here the significant lack of catalytic activity when thiazolin-2-ylidenes were generated under conditions that precluded the formation of **2**. In these experiments, thiazolin-2-ylidenes were generated by desilylation of a 2-(trimethylsilyl)thiazolium ion **9** with fluoride ion (Scheme IV).

Attempts to prepare pure salts of 3,4,5-trimethyl-2-silylthiazolium ion failed because even the triflate was too reactive, and our preparations always contained some of the (2-H) thiazolium salt.[26-28] We therefore decided to study the more stable 3-methyl-2-(trimethylsilyl)benzothiazole derivatives,[29] recognizing that the catalytic activity of benzothiazolium salts[6] is known to be lower than that of simpler thiazolium salts.

Catalytic activity was observed in experiments c, d, and h, in which the presence of **2** was to be expected: in experiment d, it was introduced directly, and in experiments c and h it was formed by reaction between the 3-methylbenzothiazolin-2-ylidenes, generated either by deprotonation (c) or by desilylation (h), and the 3-methylbenzothiazolium ions.

Contrarywise, no catalytic activity was observed in experiments a, b, and e–g. This outcome in control experiments a and b was to be expected, but it was important to confirm that benzothiazolium ions could not induce any catalytic activity. In experiments e–g, no **2** should be present. According to the reported chemical behavior of 2-silylonium ions toward nucleophiles,[30,31] formation of bis(methylbenzothiazolin-2-ylidene) cannot take place by reaction between 3-methylbenzothiazolin-2-ylidene (generated by desilylation) and 3-methyl-2-(trimethylsilyl)-benzothiazolium ions.

**Table I. Calculated Bond Orders of 10 and 11**

| | 10 | 11 |
|---|---|---|
| C(2)–N | 0.98 | 0.99 |
| C(4)–N | 1.02 | 1.02 |
| C(2)–C(7) | 1.74 | 1.74 |
| C(4)–C(5) | 1.80 | 1.80 |

## Theoretical Results

MNDO calculations were carried out on (*Z*)-2-(hydroxymethylene)-3-methylthiazoline (**10**), and (*E*)-2-(hydroxymethylene)-3-methylthiazoline (**11**). These molecules can be represented by the resonance structures shown in Scheme V.

The so-called Kekulé Index (KI), introduced by Graovac and co-workers[32] and generalized by Moyano and Paniagua,[33] is a convenient indicator of the relative importance of the valence-bond structures used in a resonance de-

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Table II. Orbital Delocalizations in 10 and 11

| | enamine-like | | enol-like | |
|---|---|---|---|---|
| | 10 | 11 | 10 | 11 |
| N | 91.11 | 90.32 | | |
| O | | | 95.86 | 95.81 |
| C(2) | 1.62 | 1.82 | 1.90 | 1.91 |
| C(4) | 2.78 | 3.18 | | |
| C(5) | 1.68 | 1.78 | | |
| C(7) | 1.62 | 1.76 | 2.13 | 2.17 |

scription of a given molecule. Furthermore, the following equation has been proposed[34] for estimation of the weight ($W$) of each structure.

$$KI = 1 + 0.024 \ln W$$

Application of this equation to the results of MNDO calculations gave the values for KI and W shown in Scheme V.

From an electronic point of view, 2-(hydroxymethylene)-3-methylthiazolines can be considered as normal enol compounds, which can be represented by their uncharged covalent structures. Enamine-like delocalization toward C(5) (**10d** and **11d**) is more important than toward C(2) (**10b** and **11b**). The calculated bond orders (Table I) support this conclusion.

Enol-like delocalization (**10c** and **11c**), which puts a negative charge on C(2), is of the same order of importance as enamine-like delocalization. These two types of delocalizations are reflected in the percent composition of the corresponding molecular orbitals (Table II).

## Conclusion

We conclude that, at least in an aprotic medium, in the benzoin condensation catalyzed by either thiazolium salts plus base or by bis(thiazolin-2-ylidene)s, the actual catalytic species are the bis(thiazolin-2-ylidene)s, and that **5** are more likely intermediates than the Breslow intermediates **4**.

## Experimental Section

All experiments were conducted in anhydrous dioxane (10 mL) and an argon atmosphere at 100 °C during 24 h.

Bis(3-methylbenzothiazolin-2-ylidene) was prepared as described in the literature;[35] before being used, it was washed with cold anhydrous acetone and dried in an argon atmosphere without heating.

3-Methyl-2-(trimethylsilyl)benzothiazolium salt was prepared in situ, in an inert atmosphere at 0 °C, as described in the literature[29] but with methyl trifluoromethanesulfonate instead of methyl fluorosulfonate as the quaternizing agent (*CAUTION*: see ref 36). The manipulation of the 2-TMS-thiazolium salt was conducted in the most anhydrous conditions and lowest temperature possible to avoid thermal decomposition and/or hydrolysis by traces of water.

The GLC benzoin quantification of each experiment was realized from an aliquot taken after 24 h of reaction. A Hewlett-Packard 5890 chromatograph fitted with a Hewlett-Packard 19091/102 high-performance capillary cross-linked column, 5% phenylmethylsilicone, 25 m, 0.2 mm internal diameter and connected to a Hewlett-Packard 3390A integrator was used. A temperature program of 90 °C for 2 min and then 16 °C/min up to 300 °C and decanol as internal standard were employed.

**Computational Procedure.** All numerical values were obtained by using the MNDO method[37] as implemented in a locally modified version of the MOPAC program,[38] with standard parameters.[39] All equilibrium geometries were determined by minimizing the total energy with respect to all geometrical variables by using the standard DFP algorithm.[40]

**Experiments Performed.** (a) Benzaldehyde (1.042 g, 9.8 mmol) and 3-methylbenzothiazolium iodide (262 mg, 0.98 mmol). Benzoin yield: 0%. (b) Benzaldehyde (1.042 g, 9.8 mmol), 3-methylbenzothiazolium iodide (262 mg, 0.98 mmol), and sodium fluoride (400 mg, 9.5 mmol). Benzoin yield: 0%. (c) Benzaldehyde (1.042 g, 9.8 mmol), 3-methylbenzothiazolium iodide (262 mg, 0.98 mmol), ethyldiisopropylamine (378 mg, 2.9 mmol), and decanol (90 mg, 0.57 mmol). Benzoin yield: 12%. (d) Benzaldehyde (1.042 g, 9.8 mmol), bis(3-methylbenzothiazolin-2-ylidene) (232 mg, 0.98 mmol), and decanol (90 mg, 0.57 mmol). Benzoin yield: 15%. (e) Benzaldehyde (1.042 g, 9.8 mmol), 3-methyl-2-(trimethylsilyl)benzothiazolium trifluoromethanesulfonate (from 278 mg, 1.3 mmol of 2-(trimethylsilyl)benzothiazole[17]) and sodium fluoride (400 mg, 9.5 mmol). Benzoin yield: 0%. (f) Benzaldehyde (104 mg, 0.98 mmol), 3-methyl-2-(trimethylsilyl)benzothiazolium trifluoromethanesulfonate (from 278 mg, 1.3 mmol of 2-(trimethylsilyl)benzothiazole[17]) and sodium fluoride (400 mg, 9.5 mmol). Benzoin yield: 0%. (g) Octanal (142 mg, 1.1 mmol), 3-methyl-2-(trimethylsilyl)benzothiazolium trifluoromethanesulfonate (from 278 mg, 1.3 mmol of 2-(trimethylsilyl)benzothiazole) and sodium fluoride (400 mg, 9.5 mmol). Octoin yield: 0%. (h) Benzaldehyde (1.104 g, 9.8 mmol), 3-methyl-2-(trimethylsilyl)benzothiazolium trifluoromethanesulfonate (from 139 mg, 0.67 mmol of 2-(trimethylsilyl)benzothiazole), 3-methylbenzothiazolium iodide (131 mg, 0.49 mmol) and sodium fluoride (400 mg, 9.5 mmol). Benzoin yield: 17%.

**Acknowledgment.** We acknowledge gratefully the support of the "Comisiõn Asesora de Investigaciõn Cientifica y Tēcnica" (Grant No. 575/84) and Dr. F. Geijo for his colaboration in performing the MNDO calculations.

**Registry No.** **10**, 115561-07-4; **11**, 115561-08-5; **12**, 115561-09-6; benzaldehyde, 100-52-7; 3-methylbenzothiazolium iodide, 2786-31-4; benzoin, 119-53-9; bis(3-methylbenzothiazolin-2-ylidene), 2786-70-1; 3-methyl-2-(trimethylsilyl)benzothiazolium trifluoromethanesulfonate, 115561-10-9; 2-(trimethylsilyl)benzothiazole, 32137-73-8; methyl trifluoromethanesulfonate, 333-27-7.

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