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The Thiazolium Catalyzed Benzoin Condensation with Mild Base Does not Involve a "Dimer" Intermediate

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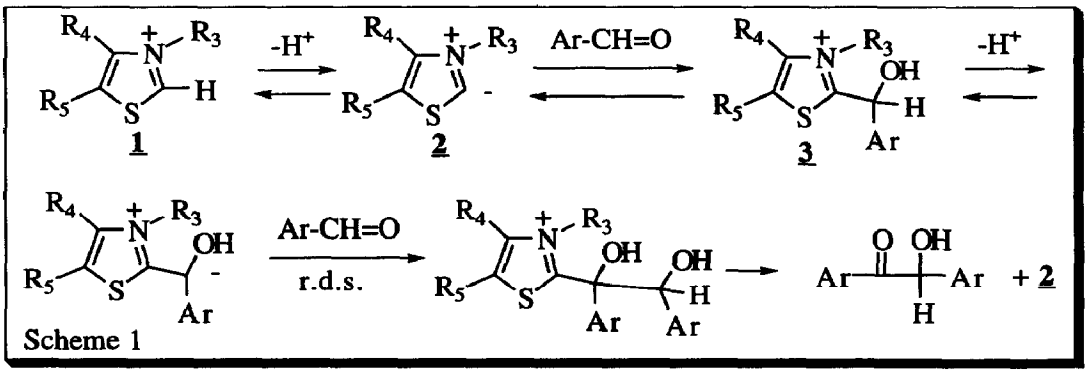
Abstract: Kinetic studies show that the benzoin condensation catalyzed by 3,4,5-trimethylthiazolium iodide and triethylamine in DMSO has a transition state with two benzaldehyde and one thiazolium components, while the conversion of nitrobenzaldehyde to the thiazolium adduct is kinetically first order in thiazolium salt and aldehyde. These findings exclude proposals that thiazolium dimers are the true catalytic species.

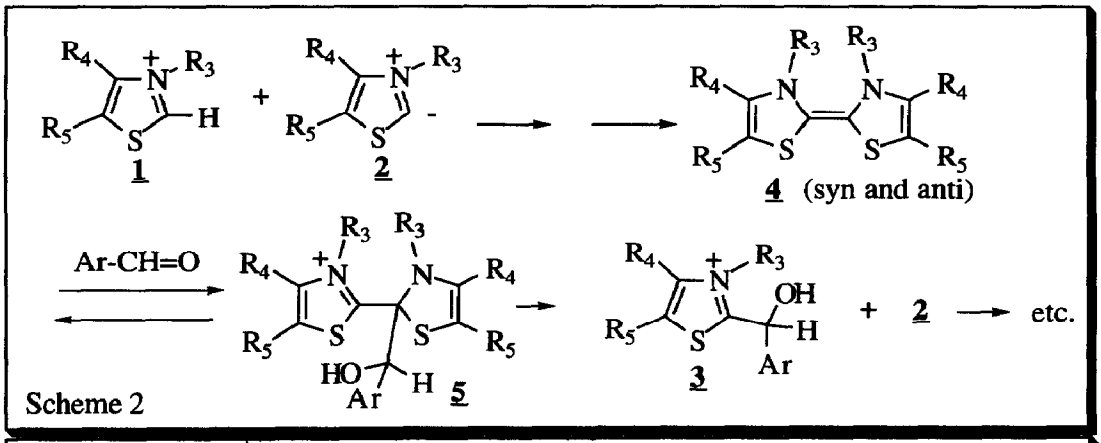
With the discovery that salts of thiazolium cations **1** are in reversible equilibrium with the corresponding ylides **2**, we proposed many years ago[1] that the benzoin condensation catalyzed by thiazolium salts in mild base proceeded by Scheme 1, via adduct **3**, an adaptation of the well-established Lapworth mechanism[2] for $^-$CN catalysis of the benzoin condensation. The biochemical functions of thiamine pyrophosphate (ThPP) were also explained in terms of the reactions of ylide **2**.

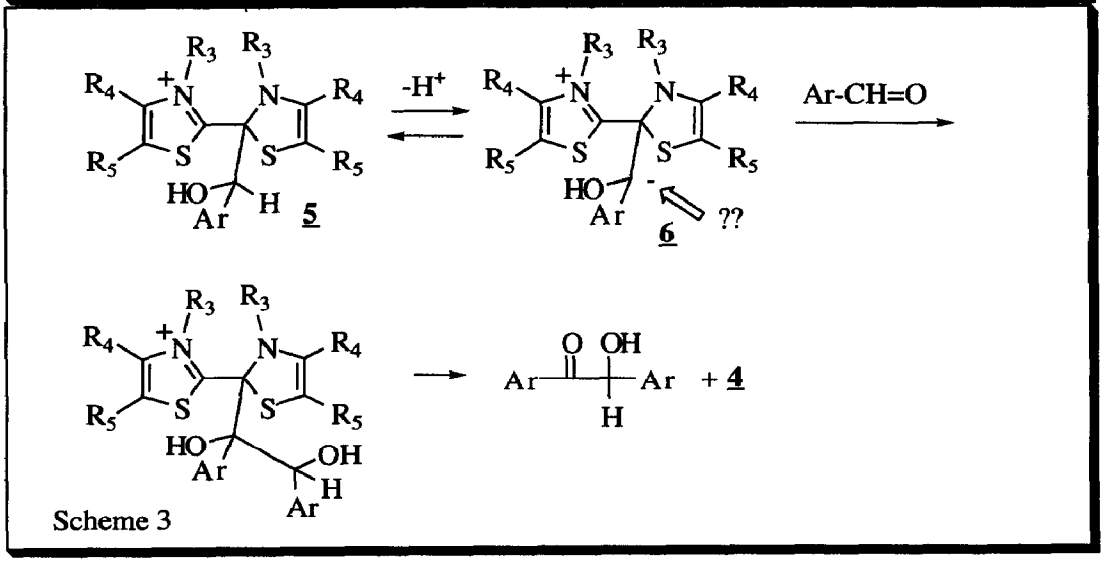


Scheme 1

When thiazolium salts are treated with strong base in non-aqueous solvents they couple to form dimers[3] **4**. It was found that such dimers are also catalysts of the benzoin condensation. In the benzothiazolium and naphthothiazolium series they are actually more effective than are the corresponding monomeric thiazolium salts.[4] With simple thiazolium salts[5] it was reported that dimerization of **1** to **4** slowed the rate of benzoin condensation, while in another report the dimers were stated to give better yields than did the simple thiazolium salts.[6] Castells has described[6,7] alternatives to Scheme 1, based in part on these findings. In Scheme 2—related to the work of Lemal[8]—the dimer **4** reacts as a nucleophilic enamine to form an intermediate **5** that fragments (in a reversal of the **1** plus **2** type of dimerization) to form the same intermediate **3** that we had proposed in Scheme 1. Then this

proceeds as in Scheme 1. In Scheme 3, which he prefers,[6,7,9,10] Castells suggested that no fragmentation occurs and that benzoin formation involves attack on benzaldehyde by anion **6**. He argued that monomeric **1** acts catalytically only by dimerizing to **4**, and that the true mechanism for benzoin condensation proceeds through Scheme 3, not Scheme 1.





We have now investigated the thiazolium catalyzed benzoin condensation further, using ^{1}H NMR to characterize intermediates and u.v. to follow the kinetics. The evidence clearly indicates that the mechanism of Scheme 3 is incorrect, and that under normal mild base conditions the intermediate **3** is formed as in Scheme 1, not through a preferred dimer pathway involving Scheme 2.

We followed the benzoin condensation (u.v. at 327 nm) in DMSO at 45.5 °C with 90 mM Et3N and 10 mM Et3N·HCl buffer with 500 mM benzaldehyde and 10, 20, 30, 50, and 70 mM 3,4,5-trimethylthiazolium iodide. It was reported[11] that the rate is second-order in [benzaldehyde]—changing to first order when the Et3N catalyst is buffered with Et3N·HCl— but as with CN^- catalysis[12] the kinetic situation is more complex. We find

in the NMR that intermediate **3** is rapidly formed under our initial kinetic conditions (with d_6-DMSO) before much benzoin is produced. The NMR spectrum—with singlet signals at 6.4, 3.8, 2.4, and 2.3 ppm and aromatic peaks at 7.5 ppm—is identical with that of an authentic sample, prepared by a procedure we had described earlier.[1b] In one hour ca. 70% of **3** and 30% of **1** are in semi-equilibrium; as ArCHO is consumed by benzoin formation, the **3**/**1** ratio decreases. If the rate-limiting step in Scheme 1 is the reaction of **3** with benzaldehyde, the kinetic order in [Ar-CHO] depends on the state of the thiazolium salt: first order if it is adduct **3**, second order if it is entirely **1**. Since both **1** and **3** are significantly present the reaction is of variable order between first and second, depending on [Ar-CHO], as with CN^- catalyst.[12]

We find (Figure 1) that both a first order and a second order treatment of our data fit moderately well. When we varied the concentration of the thiazolium salt, we saw by either kinetic treatment (Figure 2) that the reaction rate is first-order in [thiazolium$_{total}$]. This was also seen by Challa and Pandit for the benzoin condensation catalyzed by 3-benzyl-4-methyl-5-hydroxyethyl thiazolium chloride.[11] This excludes the mechanism of Scheme 3, since the rate determining step there involves a dimer of **1** and should show second-order kinetics in **1** unless **1** were completely converted to **4** under these conditions. However, we observe **1** and **3** by NMR but no trace of dimer **4** in our solutions. Of course Scheme 3 is quite unlikely *a priori*, since the proposed anion **6** is not significantly stabilized.

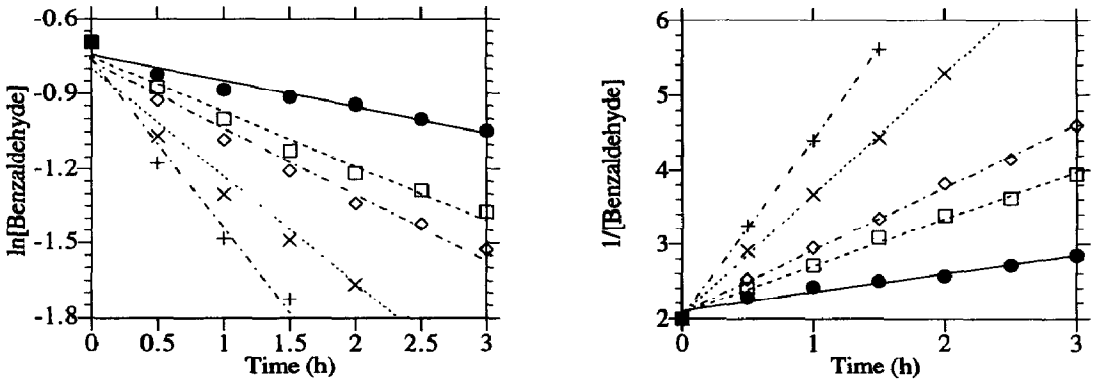


Fig. 1.-First Order (Left) and Second Order (Right) Plots of our Kinetic Data Increasing in Rate with 10, 20, 30, 50, and 70 mM Trimethylthiazolium Iodide

Scheme 2 is not excluded by the above studies by us and by Challa and Pandit;[11] it is simply another way to get from **1** to our proposed intermediate **3**, whose reaction with another benzaldehyde is rate determining and has the correct kinetic order. As we described, **3** is in reversible semi-equilibrium with starting materials. In order to resolve the kinetic ambiguity between Schemes 1 and 2, we need a process in which the formation of **3** is rate determining. In fact, we have described such a process previously.[13]

When **3** is formed in the presence of strong oxidants it can oxidize. We had followed the rate of this overall reaction using ferricyanide ion to oxidize p-nitrobenzaldehyde, a process catalyzed by thiazolium salts.[13] In 60:40 DMSO/H_2O 0.5 M in pH 8 phosphate buffer with sufficient $Fe(CN)_6^{3-}$ the reaction rate showed first

order dependence on [1], first order dependence on the aldehyde, and zero-order dependence on $Fe(CN)_6^{3-}$. The rate determining step is formation of 3, which is then rapidly oxidized. We have reconfirmed these findings. Thus under these mild-base conditions intermediate 3 is formed directly from the addition of ylide 2 to the aldehyde—as in Scheme 1—and not via a dimer. Scheme 2 would require that the rate of formation of 3 be second-order in 1.

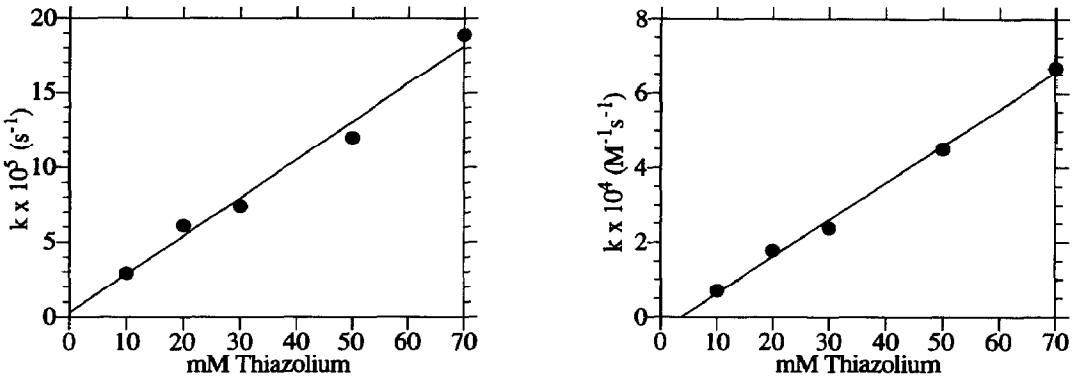


Fig. 2.-First Order (Left) and Second Order (Right) Calculated Rate Constants from the Data of Figure 1 as a Function of Thiazolium Concentration

The reaction mechanism in strong base—in which 1 can be converted to the dimers 4—is also of interest, but we have no kinetic evidence on this. The most likely process in any case is that of Scheme 2 when strong base is used to convert 1 first to its dimer 4. However, our studies show that under the mild base conditions relevant to biological systems—and also of course in the biochemical systems themselves, in which a single thiamine pyrophosphate is bound in the enzyme[14]—dimers of thiazolium ions are not involved. Thus Scheme 1 still seems the most likely for the benzoin condensation under these conditions.

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References

1. (a) Breslow, R. *J. Amer. Chem. Soc.* **1958**, *80*, 3719. (b) Breslow, R.; McNelis, E. *J. Amer. Chem. Soc.* **1959**, *81*, 3080.
2. Lapworth, A. J. *J. Chem. Soc.* **1903**, *83*, 995.
3. Wanzlick, H.-W.; Kleiner, H. J. *Angew. Chem.* **1963**, *75*, 1204.
4. Lachmann, B.; Steinmaus, H.; Wanzlick, H.-W. *Tetrahedron* **1971**, *27*, 4085.
5. Yano, Y.; Tamura, Y.; Tagaki, T. *Bull. Chem. Soc. Jpn*, **1980**, *53*, 740.
6. Castells, J.; Lopez-Calahorra, F.; Geijo, F.; Perez-Dolz, R.; Bassedas, M. *J. Heterocycl. Chem.* **1986**, *23*, 715.
7. Castells, J.; Lopez-Calahorra, F.; Domingo, L. *J. Org. Chem.* **1988**, *53*, 4433.
8. Lemal, D. M.; Lovald, R. A.; Kawano, K. I. *J. Amer. Chem. Soc.* **1964**, *86*, 2518.
9. Castells, J.; Domingo, L.; Lopez-Calahorra, F.; Marti, J. *Tetrahedron Lett.* **1993**, *34*, 517.
10. Marti, J.; Castells, J.; Lopez-Calahorra, F. *Tetrahedron Lett.* **1993**, *34*, 521.
11. van den Berg, H. J.; Challa, G.; Pandit, U. K. *J. Mol Cat.* **1989**, *51*, 1.
12. Kübrich, J. P.; Schowen, R. L.; Wang, M.-S.; Lupes, M. E. *J. Amer. Chem. Soc.* **1971**, *93*, 1214.
13. Hilvert, D.; Breslow, R. *Bioorg. Chem.* **1984**, *12*, 206.
14. Schneider, G.; Lindqvist, Y. *Bioorg. Chem.* **1993**, *21*, 109.

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