Pergamon

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The Mechanism of Thiazolium Catalysis

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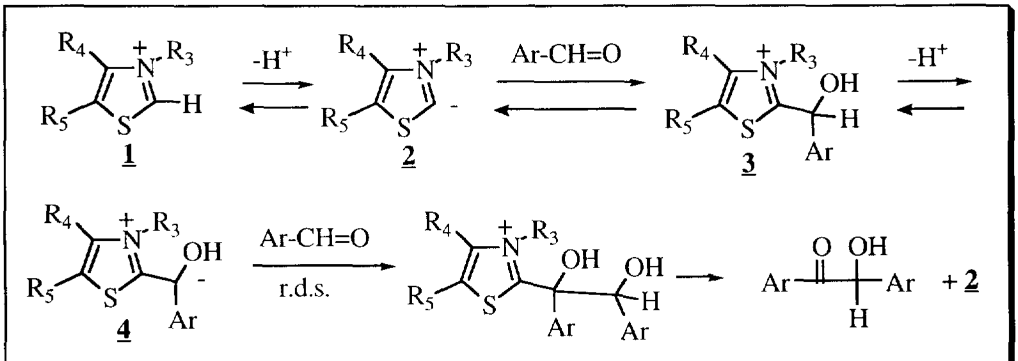
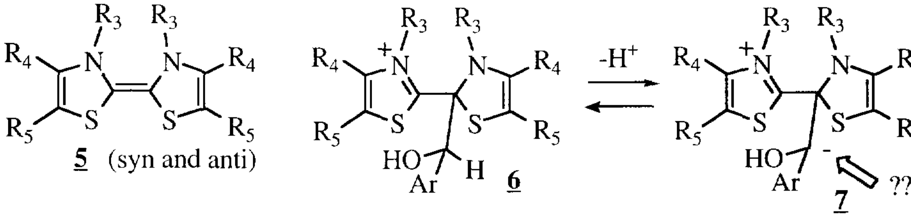
Abstract. Contrary to recent reports, the catalysis of the benzoin condensation is first order in thiazolium ion, even based on the data recently reported by others. Thus there is no need to propose an unusual anion intermediate in the reaction.

Some time ago we described studies on the benzoin condensation catalyzed by thiazolium ions **1**, in which the key point was that the thiazolium C-2 proton is easily ionized, and the resulting anion **2** adds to benzaldehyde to form intermediate **3**.[1] This then forms an anion **4** which is well stabilized by conjugation, and which adds to a second benzaldehyde carbonyl in a step that is normally rate determining for benzoin formation (Scheme 1). This mechanism has been well accepted, and is the basis of our elucidation of the mechanism of action of thiamine pyrophosphate as coenzyme in various biochemical reactions.[2] However, recently Marti et al proposed that the true mechanism of the benzoin condensation involved dimerization of the thiazolium ion to **5**, and its addition to benzaldehyde to form **6**.[3] One could imagine that **6** might fragment to form **3**, but we showed that this is not the mechanism under normal conditions.[4] Instead, the formation of intermediate **3** occurs in a process that is kinetically first order in thiazolium ion under conditions in which little of **5** is present.

Marti et al proposed that **6** is formed and that it then forms anion **7**, which adds to the second benzaldehyde in the benzoin mechanism.[3] Since anion **7** does not have the structural features needed to be a reasonably stable intermediate, this alternative mechanism was unlikely at best. However, we were able to exclude this proposed mechanism by showing that the benzoin condensation is clearly first order kinetically in thiazolium ion.[4] We pointed out[4] that Pandit had also shown[5] that the reaction was first order in thiazolium ion.



Scheme 1



This should have ended the matter, but Lopez-Calahorra published a restudy of the kinetics and stated that he could not distinguish between first and second order behavior on the basis of his data.[6] He then published a renewed proposal of the mechanism involving anion **7**, in a paper[7] in which he did not refer to the evidence from our laboratory or from Pandit that the reaction was first order in thiazolium ion. As support for his unusual mechanism he also asserted[7] that his previous study[6] had established that the reaction was second order in thiazolium ion, in contrast to what had been stated[6] in his original paper. Since this misrepresentation may confuse the unwary, we have plotted his kinetic data[6] in Figure 1, and done a computer generated best fit of the data to a first order and a second order dependence on thiazolium ion. The plots fully support the evidence from our laboratory and that of Pandit that the reaction is first order in thiazolium ion. Our original mechanism of Scheme 1 is thus still the most likely. In particular, an alternative involving anion 7 is excluded.

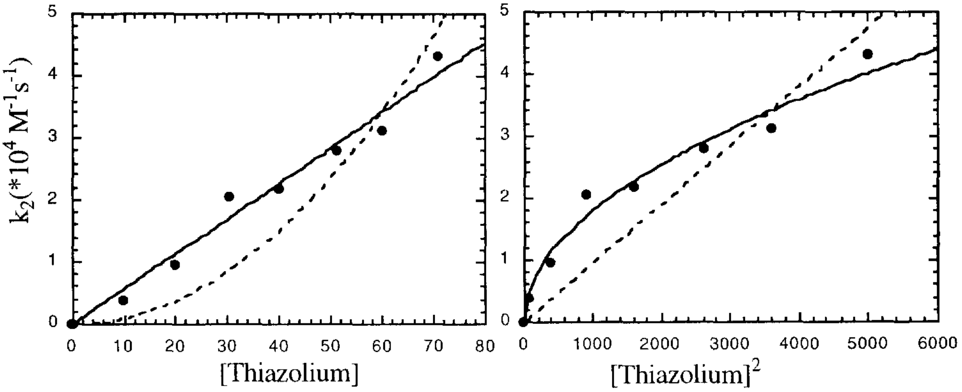


Figure 1. Plots of the second order rate constants versus thiazolium ion (left) and thiazolium ion squared (right). The solid lines are the best fit for a reaction first order in thiazolium ion, while the dashed lines are the best fit of second-order curves to the data. The solid lines, with R = 0.988, are clearly in better accord with the data than the dashed lines, with R = 0.908. Data from reference 6.

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