The Effect of Strain on the Catalytic Reactions of Bridged Thiazolium Salts as Models of Thiamin

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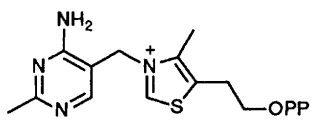
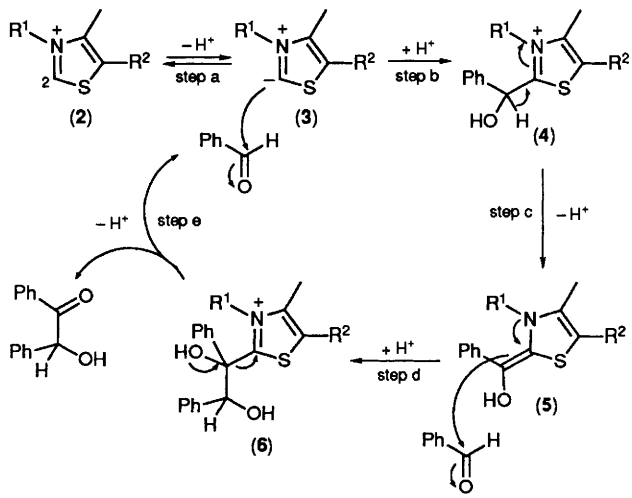
The reactivity of bridged thiazolium salts (**9**) and (**10**) has been studied; the model (**9**) with the shorter bridge is unable to catalyse the benzoin condensation reaction and it was shown that this is due to failure of the condensation step (**5**) → (**6**), probably owing to the effects of strain.

Thiamin pyrophosphate (**1**) is the cofactor used in a number of enzymic reactions in which bonds adjacent to a carbonyl are made or broken.[1] Synthetic thiazolium salts are able to catalyse the same type of reactions non-enzymically. The mechanism for the benzoin condensation, shown in Scheme 1, was first suggested by Breslow, who showed that the hydrogen on C-2 of thiamin and other thiazolium salts (**2**) exchanged readily in D_2O at neutral pH, presumably *via* the ylide (**3**).[2]

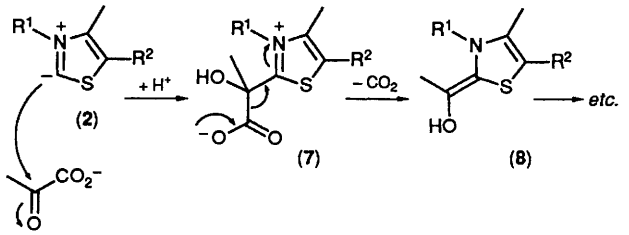
It has been suggested that pyruvate decarboxylase might enhance its catalytic rate by exerting strain on the thiazolium ring of thiamin pyrophosphate (**1**) when it is bound at the active site, tending to bend it out of planarity. This, it was argued, would increase the rate of the decarboxylation step



(**1**)



Scheme 1. Mechanism for the benzoin condensation catalysed by a thiazolium salt.



Scheme 2. Mechanism for the decarboxylation of pyruvate.

(Scheme 2) as the product (**8**) would be more easily distorted from planarity than the aromatic thiazolium ring of (**7**).[3] We have, therefore, set out to test this theory by the synthesis, which has already been described,[4] of thiazolium salts (**9**) and (**10**), strained by a short bridge between N-3 and C-5. We describe here our investigations into the catalytic reactions of these thiazolium salts.

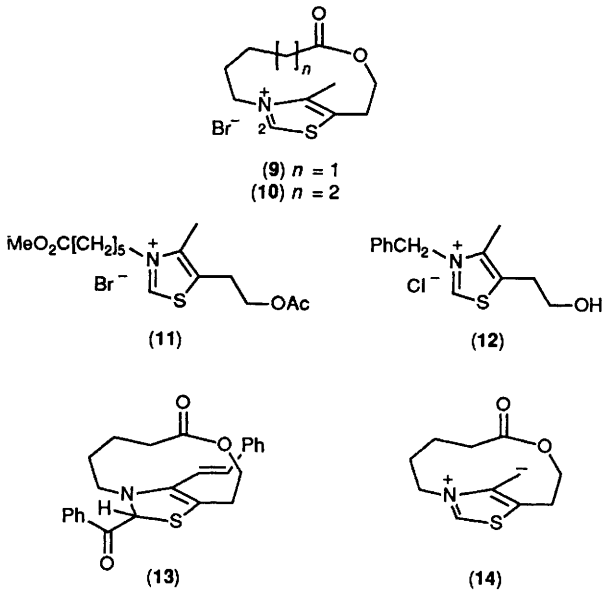
The two bridged thiazolium salts were compared as catalysts for the benzoin condensation with two other unbridged thiazolium salts, (**11**)† and (**12**).[5] The reaction was followed both by NMR spectroscopy (in deuteriomethanol) and by GC. The results from both techniques were qualitatively the same: the standard thiazolium salt (**12**) reacted fastest, the longer bridged thiazolium salt (**10**) reacted at about half this rate, and the unbridged thiazolium salt (**11**) reacted at a rate intermediate between these two. The shorter bridged thiazolium salt (**9**), however, gave no trace of benzoin by either method. By GC the amount of benzaldehyde decreased by about 20% and then remained constant. This decrease corresponds approximately to the amount of catalyst present.

The inability of the shorter bridged thiazolium salt (**9**) to catalyse the benzoin condensation could be because any one of the five steps shown in Scheme 1 failed to proceed. It was necessary, therefore, to look at each step in turn, as far as that is possible.

The rate of deprotonation at C-2 of the thiazolium salt (step a in Scheme 1) is simply measured by following the exchange of H-2 by NMR spectroscopy. It was found that the rates of exchange for the bridged compounds, (**9**) and (**10**), were indistinguishable from that of (**12**), whereas the rate for the unbridged model (**11**) was marginally slower ($k_{rel.}$ 0.7). Hence the inability of thiazolium salt (**9**) to catalyse the benzoin condensation is not due to a failure to generate the corresponding ylide.

The rate of formation of the 'active aldehyde' intermediate (**5**) can be measured by following its rapid oxidation by compounds such as flavins,[6] quinones, or ferricyanide.[7] The rate of oxidation of *m*-chlorobenzaldehyde by ferricyanide, catalysed by each of the thiazolium salts, was measured by following the disappearance of the ferricyanide absorbance at 420 nm.[7] The rates were approximately equal with all four thiazolium salts as catalysts. The shorter bridged catalyst was, in fact, marginally faster than the other three ($k_{rel.}$ 1.2). It is clear, therefore, that the first three steps (a, b, and c) of the benzoin mechanism operate quite normally with the shorter bridged thiazolium salt (**9**) as catalyst.

In order to determine whether it is step d or e which does not proceed with catalyst (**9**), the reaction mixture for a benzoin condensation was made up containing a relatively



large quantity of this catalyst. After 5 h the mixture was evaporated to dryness and the products were purified by preparative TLC. A new bright yellow compound was isolated, whose structure proved to be a keto-dihydrothiazole (**13**), derived from the catalyst (**9**) in 20% yield.‡

Keto-dihydrothiazoles such as (**13**) would not normally be expected to be stable as they would readily revert by enolization to intermediates such as (**5**) and thence to (**4**). We are not aware of such a compound ever having been reported before. It seems clear that the isolation of (**13**) in this case as a stable compound is due to the strain of the short bridge. This strain can be partly relieved in compounds where the nitrogen atom can adopt tetrahedral as opposed to trigonal geometry. Thus formation of (**13**) is favoured whereas reversion of an intermediate such as (**5**) to a thiazolium ion (**4**) is not. Similarly in order to proceed with the benzoin condensation, attack of (**5**) on the second aldehyde molecule to form (**6**) also requires that the nitrogen atom becomes planar and is thus disfavoured by the shorter bridge.

A surprising feature of by-product (**13**) is the styryl side-chain. This is presumably formed by condensation between the methyl group of the catalyst (**9**) and a benzaldehyde molecule but it is not obvious at what stage this occurs. It is possible that deprotonation of the thiazolium salt can occur to generate the dipolar species (**14**), which then attacks the aldehyde. Exchange of the protons on the methyl group of 4-methylthiazolium ions under basic conditions has been reported previously.[8] As the yield of this product is only 20%, it is likely that the majority of the catalyst did not react in this manner. No other compound derived from the catalyst was isolated, however, perhaps because of high polarity or lack of UV absorbance.

The anomalous behaviour of the strained, shorter bridged thiazolium salt (**9**) is consistent with the suggestion that the effect of this type of strain is to disfavour intermediates in which the nitrogen atom has to be sp^2 hybridized and planar, and to favour intermediates in which it can be more easily distorted out of planarity. This effect would be expected to

† Compound (**11**) was synthesized by alkylation of the corresponding thiazole with methyl 6-bromohexanoate.

‡ *Selected spectral data* for (**13**): M^+, *m/z* 419.1531; $\lambda_{max.}$ 284 nm; $\nu_{max.}$ 1720, 1680, and 1600 cm^{-1}; δ_H 7.07 and 6.76 (each d, *J* 16 Hz, CH=CH) and 5.93 (s, 2-H); δ_C 187.6 (ketone) and 72.8 (2-CH).

facilitate the loss of CO_2 in the decarboxylation of pyruvate (Scheme 2). In this step the nitrogen atom goes from being obligatorily sp^2 hybridized to a situation where it could be sp^3 hybridized if necessary. Thus the results described here support the theory that strain on the thiazolium ring could be a factor used by pyruvate decarboxylase to enhance its catalytic rate.

We thank the SERC for a studentship to D. H. C. S.

Received, 27th March 1990; Com. 0/01343I

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